

Thalidomide:

Class:

□ Angiogenesis Inhibitor; Antineoplastic Agent; Immunomodulator, Systemic

Indications:

- Treatment of newly-diagnosed multiple myeloma;
- treatment and maintenance of cutaneous manifestations of erythema nodosum leprosum (ENL)

Unlabeled use :

- Treatment of refractory Crohn's disease;
- treatment of chronic graft-versus-host disease (GVHD) in hematopoietic stem cell transplantation;
- AIDS-related aphthous stomatitis;
- Waldenström's macroglobulinemia;
- maintenance therapy of multiple myeloma (following autologous stem cell transplant);
- systemic light chain amyloidosis

Available dosage form in the hospital:

- 100 mg tablet

Trade Names:

Inmunoprin , Thado , Thalix , **Thalomid**

Dosage:

-Cutaneous ENL: Oral: Initial: 100-300 mg once daily

**Adjustments to initial dose:*

- Patients weighing <50 kg: Initiate at lower end of the dosing range
- Severe cutaneous reaction or patients previously requiring high dose may be initiated at 400 mg daily; doses may be divided, but taken 1 hour after meals

**Duration and tapering/maintenance:*

- Maintenance: Dosing should continue until active reaction subsides (usually at least 2 weeks), then tapered in 50 mg decrements every 2-4 weeks
- Patients who flare during tapering or with a history of requiring prolonged maintenance should be maintained on the minimum dosage necessary to control the reaction. Efforts to taper should be repeated every 3-6 months, in decrements of 50 mg every 2-4 weeks.

-Multiple myeloma: Oral: **Note:** Details concerning dosing for multiple myeloma with combination regimens should also be consulted.

- 200 mg once daily at bedtime (in combination with dexamethasone 40 mg daily on days 1-4, 9-12, and 17-20 of a 28-day treatment cycle)
- In combination with bortezomib and dexamethasone (unlabeled combination): Induction therapy: 100 mg once daily for the first 14 days, then 200 mg once daily for 3 (21-day) cycles (Cavo, 2010) **or** 100 mg once daily for up to 8 (21-day) cycles (Kaufman, 2010)

- In combination with melphalan and prednisone (unlabeled combination in U.S.): 200-400 mg once daily (Facon, 2007) **or** 100 mg once daily (Palumbo, 2008)
- ***Canadian labeling*: Adults ≥ 65 years: 200 mg once daily; maximum: 12 six-week cycles (in combination with melphalan and prednisone)
- Multiple myeloma, maintenance (following autologous stem cell transplant; unlabeled use)*: Oral: 200 mg once daily starting 3-6 months after transplant; continue until disease progression or unacceptable toxicity (Brinker, 2006) or 100 mg once daily starting 42-60 days following transplant; increase to 200 mg once daily after 2 weeks if tolerated; continue for up to 12 months (in combination with prednisolone) (Spencer, 2009)
- AIDS-related aphthous stomatitis (unlabeled use)**: Oral: 200 mg once daily at bedtime for up to 8 weeks, if no response, then 200 mg twice daily for 4 weeks (Jacobson, 1997)
- Chronic graft-versus-host disease (refractory), treatment (unlabeled second-line use; optimum dose not determined)**: Oral: Initial: 100 mg once daily at bedtime, with dose escalation up to 400 mg daily in 3-4 divided doses (Wolff, 2010) **or** Initial: 50-100 mg 3 times daily; maximum dose: 600-1200 mg daily (Kulkarni, 2003) **or** 200 mg 4 times daily (dose adjusted to goal thalidomide concentration of ≥ 5 mcg/mL 2 hours postdose) (Vogelsang, 1992) **or** 100-300 mg 4 times daily (Parker, 1995)
- Crohn's disease, refractory (unlabeled use)**: Oral: 50-100 mg once daily at bedtime (Vasiliauskas, 1999) **or** 200-300 mg once daily at bedtime (Ehrenpreis, 1999)
- Systemic light chain amyloidosis (unlabeled use)**: Oral: 200 mg once daily (starting dose 50-100 mg once daily; titrate at 4-week intervals) in combination with cyclophosphamide and dexamethasone (Wechalekar, 2007)
- Waldenström's macroglobulinemia (unlabeled use)**: Oral: 200 mg once daily for up to 52 weeks (in combination with rituximab) (Treon, 2008)

Geriatric

Refer to adult dosing.

Renal Impairment:

No adjustment is required for patients with renal impairment and on dialysis (per manufacturer). In a study of 6 patients with end-stage renal disease on dialysis, although clearance was increased by dialysis, a supplemental dose was not needed (Eriksson, 2003).

Multiple myeloma: An evaluation of 29 newly-diagnosed myeloma patients with renal failure (serum creatinine ≥ 2 mg/dL) treated with thalidomide and dexamethasone (some also received cyclophosphamide) found that toxicities and efficacy were similar to patients with normal renal function (Seol, 2010). A study evaluating induction therapy with thalidomide and dexamethasone in 31 newly-diagnosed myeloma patients with renal failure ($Cl_{cr} < 50$ mL/minute), including 16 patients with severe renal impairment ($Cl_{cr} < 30$ mL/minute) and 7 patients on chronic hemodialysis found that toxicities were similar to patients without renal impairment and that thalidomide and dexamethasone could be administered safely (Tosi, 2009).

Hepatic Impairment:

No dosage adjustment provided in manufacturer's labeling (has not been studied). However, thalidomide does not appear to undergo significant hepatic metabolism.

Dosing: Adjustment for Toxicity

-ANC $\leq 750/mm^3$: Withhold treatment if clinically appropriate

-Multiple myeloma:

-*U.S. labeling*: Constipation, oversedation, peripheral neuropathy: Temporarily withhold or continue with a reduced dose

-Canadian labeling:

- ANC $<1500/\text{mm}^3$: Withhold melphalan and prednisone for 1 week; resume melphalan and prednisone after 1 week if ANC $>1500/\text{mm}^3$ **or** if ANC 1000-1500/ mm^3 reduce melphalan dose by 50% **or** if ANC $<1000/\text{mm}^3$ adjust chemotherapy dose based on clinical status of patient.
- Constipation, oversedation: Temporarily withhold thalidomide treatment or continue with a reduced dose
- Peripheral neuropathy, Grade 1 (paresthesia, weakness and/or loss of reflexes) without loss of function): Evaluate patient and consider dose reduction with worsening of symptoms; symptom improvement may not follow dose reduction, however.
- Peripheral neuropathy, Grade 2 (interferes with function but not with daily activities), Grade 3 (interferes with daily activities), or Grade 4 (disabling neuropathy): Discontinue thalidomide treatment
- Thromboembolic events: Withhold therapy and initiate standard anticoagulant treatment; may resume thalidomide therapy at original dose following stabilization of patient and resolution of thromboembolic event; maintain anticoagulant treatment for duration of thalidomide therapy

-Unlabeled recommendation (Richardson, 2012): Peripheral neuropathy:

- Grade 1: Reduce dose by 50%
- Grade 2: Temporarily interrupt therapy; once resolved to \leq grade 1, resume therapy with a 50% dosage reduction (if clinically appropriate)
- Grade 3 or higher: Discontinue therapy

Common side effect:

- Cardiovascular: Edema (57%), thrombosis/embolism (23%; grade 3: 13%, grade 4: 9%), hypotension (16%)
- Central nervous system: Fatigue (79%; grade 3: 14%, grade 4: 3%), somnolence (36% to 38%), dizziness (4% to 20%), sensory neuropathy (54%), confusion (28%), anxiety/agitation (9% to 26%), fever (19% to 23%), motor neuropathy (22%), headache (13% to 19%)
- Dermatologic: Rash/desquamation (21% to 30%; grade 3: 4%), dry skin (21%), maculopapular rash (4% to 19%), acne (3% to 11%)
- Endocrine & metabolic: Hypocalcemia (72%)
- Gastrointestinal: Constipation (3% to 55%), nausea (4% to 28%), anorexia (3% to 28%), weight loss (23%), weight gain (22%), diarrhea (4% to 19%), oral moniliasis (4% to 11%)
- Hematologic: Leukopenia (17% to 35%), neutropenia (31%), anemia (6% to 13%), lymphadenopathy (6% to 13%)
- Hepatic: AST increased (3% to 25%), bilirubin increased (14%)
- Neuromuscular & skeletal: Muscle weakness (40%), tremor (4% to 26%), weakness (6% to 22%), myalgia (17%), paresthesia (6% to 16%), arthralgia (13%)
- Renal: Hematuria (11%)
- Respiratory: Dyspnea (42%)
- Miscellaneous: Diaphoresis (13%)

Pregnancy Risk Factor: X