Regimen Monograph

A - Regimen Name

THAL Regimen

Thalidomide

Disease Site	Hematologic - Multiple Myeloma
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	For the treatment of relapsed or refractory multiple myeloma.

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B - Drug Regimen

thalidomide	50 to 200* mg	PO	Daily

(This drug is not currently publicly funded for this regimen and intent)

*Maximum starting dose in patients ≤ 75 years: 200 mg daily; for patients > 75 years: 100 mg daily
Thalidomide is only available through a controlled distribution program- RevAid®. For more information, please call 1-888-revaid1 (1-888-738-2431) or visit www.revaid.ca

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

Other Supportive Care:

- Prophylactic anticoagulants should be used, especially in patients with other risk factors and for at least the first five months of treatment.
- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered.

Dosage with toxicity

Dose levels (thalidomide):

Dose level	Age ≤ 75 years	Age > 75 years
0	200 mg daily	100 mg daily
-1	100 mg daily	50 mg daily
-2	50 mg daily	50 mg every other day
-3	50 mg every other day	Discontinue

Toxicity	Thalidomide Dose and Action
ANC < 1.5 (x 10^9/L)	No change
Grade 3 or 4 thromboembolism	Hold, ensure adequately anticoagulated. Maintain dose level unless occurred despite adequate anticoagulation; if so, discontinue
Grade 3 neurotoxicity	Hold until resolves to ≤ grade 1, then decrease by 1 dose level
Grade 4 neurotoxicity	Discontinue
Grade 3 rash or mild hypersensitivity	Hold until rash resolves to ≤ grade 1, then decrease by 1 dose level
Grade 4 rash or severe hypersensitivity	Discontinue
Grade 3 or 4 constipation	Initiate bowel regimen and hold until resolves to ≤ grade 2, then decrease by 1 dose level
Over sedation	Consider short drug holiday or ↓ dose; may restart at the same or lower dose when recovered
Severe syncope/bradycardia	Consider ↓ dose or discontinue
Other grade 3 toxicity	Hold until resolves to ≤ grade 2 then decrease by 1 dose level
Other grade 4 toxicity	Discontinue

Hepatic Impairment

Not specifically studied in patients with hepatic impairment.

Renal Impairment

Not specifically studied in patients with renal impairment. Monitor patients with severe renal impairment as metabolites are eliminated via urine. Some data suggested that no dose modification is needed in renal impairment (including patients on dialysis); however monitor closely as there have been reports of fatal hyperkalemia in renally impaired patients.

Dosage in the Elderly

For patients older than 75, the recommended starting dose is 100 mg/day. The frequency of serious adverse effects, such as atrial fibrillation, back pain and fall, including fatal reactions was higher in patients over 75 compared to younger patients.

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F - Adverse Effects

Refer to thalidomide drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
	• Myelosuppression +/- infection, bleeding (may be severe, includes opportunistic, viral reactivation)	• Constipation • Somnolence • Peripheral and autonomic neuropathy (may be severe) • Dizziness • Tremor • Venous thromboembolism (may be severe) • Fatigue • Confusion	• Arterial thromboembolism • Cardiotoxicity • Arrhythmia • Hypersensitivity • Rash • GI obstruction / perforation • Pancreatitis • Pneumonitis • Seizure • Hepatotoxicity • Renal failure • Secondary leukemia

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G - Interactions

Refer to thalidomide drug monograph(s) for additional details

- Use with caution when combined with other neurotoxins and sedatives given increased risk of neurotoxicity and sedation

- Use beta-blockers with caution given increased risk of bradycardia
- Use with caution and consider thromboembolism prophylaxis when used with hormonal therapy, contraceptives, erythropoietic agents and corticosteroids

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H - Drug Administration and Special Precautions

Refer to thalidomide drug monograph(s) for additional details

Administration:

- Oral self-administration; taken on a specified schedule (usually once daily) preferably with a glass of water, with or without food at about the same time each day.
- Swallow capsules whole; they should not be broken, chewed, or opened.
- Thalidomide should be administered at bedtime to minimize adverse effects such as dizziness and somnolence.
- Avoid use of alcohol since this may potentiate sedation.
- Do not extensively handle the capsules. Females who may become or plan to become pregnant can handle thalidomide if they are using latex gloves.
- Remove capsule from the original packaging only at administration time. Do not put the capsule on the counter or dish/container before taking it; give the capsule directly from the packaging and place into the mouth.
- If a dose is missed, take it if it is within 12 hours from the missed dose, otherwise skip this and give the next dose as scheduled. Do not double the dose to make up for the forgotten one.
- Drug available by outpatient prescription in pharmacy registered with the RevAid® program. Please call 1-888-RevAid-1 or log onto www.RevAid.ca.

Contraindications:

- Patients with peripheral neuropathy, or with known hypersensitivity to thalidomide, lenalidomide, or pomalidomide.
- Women who are pregnant.
- Breastfeeding women.
- Patients unable to follow or comply with the required contraceptive measures (see below section regarding the RevAid® program)

Other Warnings/Precautions:

- Patients should be wearned of the risk of drowsiness, dizziness or orthostatic hypotension. Caution in patients using sedatives or alcohol.
- May increase viral load if used in patients with HIV.
- Use with caution and monitor closely in patients with previous viral infections such as HBV or

HCV.
- Use with caution in patients with risk factors for VTE or ATE, or using thrombogenic agents. Oral contraceptives should be avoided due to the increased risk of VTE.
- Use with caution in combination with corticosteroids in myeloma due to the risk of thromboembolism - consider prophylactic anticoagulation.
- Use with caution in patients with risk factors for peripheral neuropathy, taking neurotoxic drugs, or taking drugs that may cause severe skin reactions.

Pregnancy and Lactation:

- Thalidomide is contraindicated in pregnant women and in females of childbearing potential and in males who do not comply with the contraception conditions of the RevAid® program. Refer to the thalidomide drug monograph for details.
- Breastfeeding is contraindicated.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; baseline and monthly
- Liver function tests; baseline and periodic, especially in patients with pre-existing liver disorder or with concurrent use of potentially hepatotoxic medications
- Neurological exams; baseline and periodic (ie: monthly for the first 3 months, and periodically thereafter); consider using electrophysiologic testing at baseline and every 6 months.
- RevAid requirements regarding pregnancy tests for women of childbearing potential
- EKG as clinically indicated
- Hepatitis serology; if hepatitis or reactivation suspected
- Clinical assessments of bleeding, rash, constipation, CNS effects (including neuropathy, seizures, somnolence), arterial and venous thromboembolism, syncope/bradycardia, infections, hepatitis; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- HIV viral load (in HIV-seropositive patients); after the first and third months of treatment, and then every 3 months

- Renal function tests; Baseline and regular
- Seizures; as clinically indicated, especially in at risk patients

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J - Administrative Information

Outpatient prescription for home administration

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K - References

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Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. N Engl J Med 2006; 354(10): 1021-30.

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Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 Trial. J Clin Oncol 2009; 27:3664-70.

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Rajkumar SV, Rosinol L, Hussein M, et al. Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. J Clin Oncol 2008; 26(13): 2171-7.

Rajkumar SV, Blood E, Vesole D, et al. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2006; 24: 431-6.

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Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med. 1999; 341(21): 1565-71.

Spencer A, Prince HM, Roberts AW, et al. Consolidation therapy With low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol 2009; 27:1788-1793.

Stewart AK, Chen CI, Howson-Jan K, et al. Results of a multicenter randomized phase II trial of thalidomide and prednisone maintenance therapy for multiple myeloma after autologous stem cell transplant. Clin Cancer Res. 2004;10(24):8170-6.

Thalidomide drug monograph, Cancer Care Ontario.

PEBC Advice Documents or Guidelines

- Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

June 2019 Updated emetic risk category; added PEBC guideline link

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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