Regimen Monograph

A - Regimen Name

DEXALENA Regimen

Lenalidomide-Dexamethasone (oral)

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 multiple myeloma patients who are not eligible for stem cell transplant, or who have received a stem cell transplant as first-line treatment

(Refer to the ODB Formulary for funding criteria details.)

Supplementary Public Funding

lenalidomide
ODB Limited Use (lenalidomide - For the treatment of patients with multiple myeloma, who are deemed to be lenalidomide sensitive, and/or has not experienced progression while on a lenalidomide-based regimen in a treatment or maintenance setting, according to clinical criteria) (ODB Formulary)

dexamethasone
ODB - General Benefit (dexamethasone) (ODB Formulary)

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B - Drug Regimen

lenalidomide	25 mg	PO	Days 1 to 21*

*(Previously Untreated: Alternatively, cycles 1-3 may be q 35 days, where lenalidomide may be given as 25mg PO on days 1-28.)

Lenalidomide may only be prescribed and dispensed by physicians and pharmacists registered with a controlled distribution program. Patients must also be registered and meet all conditions of the program.

dexamethasone	40** mg	PO	Days 1, 8, 15, 22

**In patients > 75 years of age, the dexamethasone dose should be reduced to 20 mg once weekly

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

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:

- Patients must be registered and meet all conditions of lenalidomide's controlled distribution program, including contraception.
- Prophylaxis for tumour lysis syndrome in patients with high bulk disease.
- Prophylaxis for venous thromboembolism is recommended in patients at risk. (e.g. low dose aspirin 81-100 mg PO daily or enoxaparin 40 mg SC daily)
- Careful consideration and monitoring must be taken with erythropoietin stimulating agents (ESAs), since the concomitant use of ESAs with lenalidomide may potentiate the risk of thrombosis. RBC or platelet transfusions with lenalidomide dose reductions/interruptions may be appropriate in severe / symptomatic anemia or thrombocytopenia.
- Consider GCSF as secondary prophylaxis.
- Optimal control of thyroid function is recommended prior to starting treatment.

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.

Women of child bearing potential must have two negative pregnancy tests before initiating treatment. Assess risk of second primary malignancies prior to starting treatment.

Dosage with toxicity

Dexamethasone doses may be reduced for dexamethasone-related adverse events (i.e. hypertension, hyperglycemia, fluid retention) to improve tolerability.

Newly diagnosed (days 1-21): 25mg, 20mg, 15mg, 10mg, 5mg, 2.5mg

Previously treated (days 1-21): 25mg, 20mg, 15mg, 10mg, 5mg

Toxicity (counts x 10^9/L)	1st Occurrence	Second and Subsequent Occurrence
Hematologic Toxicity (newly diagnosed myeloma)		
Platelets < 25	Hold, restart by ↓ 5mg when platelets ≥ 50	Hold, restart by ↓ 5mg when platelets ≥ 50
ANC < 0.5 or febrile neutropenia	Hold, start G-CSF. When ANC ≥ 1, restart: • Without dose reduction if isolated neutropenia • With 5mg ↓ if other toxicity	Hold, start G-CSF, restart by ↓ 5mg when ANC ≥ 1
Hematologic Toxicity (previously treated myeloma)		
Platelets < 30	Hold, restart at 15 mg (if 25 mg starting dose) or 5mg less than the adjusted starting dose, when platelets ≥ 30.	Hold, restart by ↓ 5mg when platelets ≥ 30
ANC < 1	Hold, start G-CSF, restart when ANC ≥ 1: • Without dose reduction if isolated neutropenia. • At 15mg (if 25 mg starting dose) or 5mg less than the adjusted starting dose, if other toxicity.	Hold, start G-CSF, restart by ↓ 5mg when ANC ≥ 1
Non-Hematologic Toxicity		
≥ Grade 3 non-hematologic	Hold, restart with ↓ 1 dose level when ≤ Grade 2	
↑ LFTs	Hold Consider restarting at a lower dose when ≤ baseline levels	
Grade 2 to 3 rash	Hold or consider discontinuing Discontinue if Stevens-Johnson syndrome suspected	
Angioedema, OR Grade 4 skin rash, OR	Discontinue	

Exfoliative or bullous rash, OR Suspected Stevens-Johnson syndrome, Toxic epidermal necrolysis or DRESS	
Pneumonitis	Hold and investigate if suspected; discontinue if confirmed
Solid organ transplant rejection	Discontinue

Hepatic Impairment

Population pharmacokinetics suggest no dosage adjustment is necessary in mild hepatic impairment (total bilirubin > 1 to < 1.5 x ULN or AST > ULN). No data available for moderate to severe hepatic impairment.

Renal Impairment

Lenalidomide clearance is decreased while exposure is increased in renal impairment. No dosage adjustment is required for CrCl ≥ 60 ml/min.

Creatinine Clearance (mL/min)	**Starting dose in Multiple Myeloma patients†**
30 to < 60	10mg daily*
< 30 (not requiring dialysis)	15mg every other day
< 30 (requiring dialysis)	No phase III clinical trial experience in this setting. 5 mg once daily. On dialysis days, the dose should be administered following dialysis.

* may be escalated to 15 mg q24h after 2 cycles if patient is not responding to treatment and is tolerating the drug.
† maintain a 3 weeks on, 1 week off schedule (q28 days)

Dosage in the Elderly

For transplant ineligible, newly diagnosed myeloma patients over 75 years of age, the concomitant dexamethasone dose should be reduced by half.

The incidences of serious and non-serious adverse events are significantly higher in patients > 65

years (constipation, confusion, dyspnea, atrial fibrillation, diarrhea, fatigue, pulmonary embolism, syncope). May be related to renal impairment. Monitor geriatric patients closely, especially cardiac and renal function. Dose modification based on degree of renal impairment is required.

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F - Adverse Effects

Refer to lenalidomide, dexamethasone 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
	• Fatigue • Constipation • Diarrhea • Myelosuppression +/- infection, bleeding (may be severe) • Musculoskeletal pain, headache • Edema • Cough, dyspnea • Nausea, vomiting	• Dizziness • Rash (may be severe, SJS, TEN, DRESS) • Anorexia • Blurred vision • Dyspepsia • Hyperglycemia • Abnormal electrolytes • Dysgeusia • Depression • Insomnia • Abdominal pain • Tremor • Steroid effects (weight gain, hyperglycemia, insomnia, myopathy, cataracts, osteoporosis)	• Arterial / venous thromboembolism • Cardiotoxicity • Arrhythmia • Pneumonitis • Pancreatitis • Hypersensitivity • Hemolysis • Hepatotoxicity • Adrenal insufficiency • Hyper/ hypothyroidism • Tumour lysis syndrome • Secondary malignancy • Renal failure • Rhabdomyolysis • Cholecystitis • Solid organ transplant rejection • Viral reactivation (herpes zoster, HBV) • Peripheral neuropathy • GVHD or transplant rejection

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G - Interactions

Refer to lenalidomide, dexamethasone drug monograph(s) for additional details

- Lenalidomide is not a substrate, inhibitor or inducer of CYP450; co-administration with substrates or inhibitors of this enzyme is unlikely to result in significant drug interactions.
- Digoxin may increase C_{max}; caution and monitor digoxin levels.
- Additive risk of thromboembolism with hormonal therapy, including contraception. Caution and monitor; consider alternative contraception and prophylaxis with anticoagulants.

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H - Drug Administration and Special Precautions

Refer to lenalidomide, dexamethasone drug monograph(s) for additional details.

Administration (lenalidomide):

- Drug available by outpatient prescription in pharmacy registered with a controlled distribution program.
- Oral self-administration; swallow capsules whole; they should not be broken, chewed, or opened. Do not extensively handle the capsules.
- Give capsules preferably with water, either with or without food. Do not remove from blister packs until ready to take the dose.
  Note: Females who could become pregnant, or who plan to become pregnant can handle lenalidomide capsules if they are using latex gloves.
- If a dose is missed, it may be taken up to 12 hours after the time it is normally taken. Otherwise, skip this and take the next dose on the following day at its usual scheduled time.
- Store capsules at room temperature (15 to 30°C).

Administration (dexamethasone):

- Oral self-administration.
- Give tablets with food in the morning on specified days.
- Store at room temperature (15 to 30°C).

Contraindications:

- Patients with a hypersensitivity (including severe rash) to lenalidomide, pomalidomide, thalidomide or any ingredient in the formulation.
- Pregnant and breastfeeding women.
- Women at risk of being pregnant and male patients who do not comply with contraception requirements (see Pregnancy section).

Warnings/precautions:

- Lenalidomide contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- Use with caution and consider venous thromboembolism prophylaxis when used in combination with corticosteroids or thrombogenic agents, such as hormones and erythropoietin (see adverse effects section).
- Exercise caution in patients with risk factors for arterial thromboembolism (e.g. hypertension and hyperlipidemia), or risk factors for atrial fibrillation (e.g. electrolyte abnormalities, pre-existing heart disease, hypertension, infection).
- Use with caution in patients with high tumour burden; monitor closely and use appropriate precautions for tumour lysis syndrome.
- Use with caution and monitor closely in patients with previous viral infections such as HBV and herpes zoster.

Pregnancy & lactation

- Lenalidomide is contraindicated in pregnancy and in females and males of childbearing potential who do not comply with the contraception conditions of the controlled distribution program.

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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 weekly for the first 8 weeks, on days 1 & 15 of cycle 3, then monthly
- Liver function tests; baseline and regular
- Renal function tests; baseline and regular
- Pregnancy testing requirements for women of child-bearing potential; before treatment and as indicated
- Thyroid function tests; baseline and periodic
- Cancer screening for occurrence of second primary malignancy; assess risk prior to starting treatment, then at each visit or as clinically indicated
- Clinical assessments and grading of cardiac and respiratory symptoms, rash, diarrhea, fatigue, constipation, infection (including viral reactivation), bleeding, tumour lysis syndrome, arterial and venous thromboembolism, hyperglycemia, myopathy, gastric irritation, and mood changes, GVHD and organ transplant rejection (if applicable); at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- ECG; baseline, repeat if arrhythmia suspected
- INR in patients receiving warfarin; baseline and regular

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Lenalidomide drug monograph, Cancer Care Ontario.

Newly Diagnosed:

Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11(1):29-37.

Zonder JA, Crowley J, Hussein MA, et al. Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: a randomized Southwest Oncology Group trial (S0232). Blood 2010;116(26):5838-41.

Relapsed / Refractory:

Dimopoulos M, Chen C, Spencer A, et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 2009;23(11):2147-52.

Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma NEJM 2007; 357: 2123-32.

Stadtmauer E. et al. Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory myeloma. Eur J Haematol 2009; 82: 426-32.

Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. NEJM 2007; 357: 2133-42.

PEBC Advice Documents or Guidelines

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

May 2022 Updated distribution program info

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M - Disclaimer

Regimen Abstracts

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Regimen Monographs

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

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