Regimen Monograph

A - Regimen Name

DEXAIXAZLENA Regimen

Dexamethasone-Ixazomib-Lenalidomide (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 In combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Note: Approval was based on the initial results of a randomized, double-blind, placebo-controlled, multicentre Phase III study in patients with relapsed and/or refractory multiple myeloma who had received at least one prior line of therapy; patients who were refractory to lenalidomide or proteasome inhibitors (any line) were excluded from the study. There was a statistically significant improvement in median progression free survival of approximately 6 months compared to the placebo regimen (20.6 months vs 14.7 months).

Supplementary Public Funding **dexamethasone**
ODB - General Benefit (dexamethasone) (ODB Formulary)

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B - Drug Regimen

ixazomib	4 mg	PO	once a week on Days 1, 8, and 15
(This drug is not currently publicly funded for this regimen and intent)			
(available as 2.3 mg, 3 mg, and 4 mg capsules)			
lenalidomide[1]	25 mg	PO	once daily on Days 1 to 21
(This drug is not currently publicly funded for this regimen and intent)			
(available as 5 mg, 10 mg, 15 mg, and 25 mg capsules)			
dexamethasone	40 mg	PO	once a week on Days 1, 8, 15, and 22

[1] Lenalidomide may only be prescribed and dispensed by physicians and pharmacists registered with RevAid®. Patients must also be registered and meet all conditions of the RevAid® program.

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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: Low – No routine prophylaxis; PRN recommended

Other Supportive Care:

Consider the use of antiviral prophylaxis during ixazomib therapy to decrease the risk of herpes zoster reactivation.

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 may be considered.

Prior to initiating a new cycle of therapy:

- Absolute neutrophil count should be ≥ 1.0 x 10^9/L
- Platelet count should be ≥75 x 10^9/L
- Non-hematologic toxicities should, at the physician's discretion, generally be recovered to patient's baseline condition or ≤ Grade 1

Dosage with toxicity

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

Table 1: Dose Reduction Levels

Dose Level	Ixazomib Dose	Lenalidomide Dose
Starting Dose*	4 mg	25 mg
-1	3 mg	15 mg
-2	2.3 mg	10 mg
-3	discontinue	5 mg**

* Recommended starting dose of 3 mg in patients with moderate or severe hepatic impairment, severe renal impairment or end-stage renal disease requiring dialysis.

** Do not dose below 5 mg daily

Table 2: Dose Modification for Toxicities

An alternating dose modification approach is recommended for ixazomib and lenalidomide for overlapping toxicities (thrombocytopenia, neutropenia, rash).

Toxicity		**Action**	**Ixazomib Dose when restart**	**Lenalidomide dose when restart**
First Occurrence Platelet count < 30 x 10^9/L OR ANC < 0.5 x 10^9/L		Hold until platelets ≥ 30 AND ANC ≥ 0.5; consider adding G-CSF	No change	1 dose level ↓
Second Occurrence Platelet count < 30 x 10^9/L OR ANC < 0.5 x 10^9/L		Hold until platelets ≥ 30 AND ANC ≥ 0.5; consider adding G-CSF	1 dose level ↓	No change
Rash	Grade 2 or 3	Hold both until ≤ Grade 1	Continue at same dose. If recurs, hold until recovery and then resume with 1 dose level ↓	Resume with 1 dose level ↓ Discontinue if ≥ Grade 2 exfoliative skin toxicity or SJS/TEN
	Grade 4	Discontinue	Discontinue	Discontinue

Toxicity		**Action**	**Ixazomib Dose when restart**	**Lenalidomide Dose when restart**
Peripheral Neuropathy	Grade 1 with Pain or Grade 2	Hold ixazomib until ≤ Grade 1 without pain or patient's baseline	Resume at same dose	Continue at same dose
	Grade 2 with pain or Grade 3	Hold both until ≤ Grade 1 without pain or patient's baseline	1 dose level ↓	Consider 1 dose level ↓ if grade 3
	Grade 4	Discontinue	Discontinue	Discontinue
≥ Grade 2 VTE		Hold lenalidomide and start anticoagulants	No change	Resume when recovered at same dose
Other Grade 3 or 4 Non-Hematological Toxicities		Hold both until recovery to baseline or ≤ Grade 1	If toxicity due to ixazomib, resume at 1 dose level ↓ once recovered or discontinue	If toxicity due to lenalidomide, resume at 1 dose level ↓ once recovered or discontinue. If pneumonitis investigate and discontinue if confirmed
Increased LFTS			See table below for dosage with hepatic dysfunction	Hold until recovery then consider dose reduction

*For additional occurrences, alternate dose modification of lenalidomide and ixazomib
**Do not dose below 5 mg daily

Hepatic Impairment

Hepatic impairment	Ixazomib dose	Lenalidomide dose
mild (total bilirubin ≤ ULN and AST > ULN OR total bilirubin 1-1.5 x ULN and any AST)	no dosage adjustment required	No dose adjustment required
moderate or severe (total bilirubin > 1.5 x ULN)	3 mg	No data

Renal Impairment

Creatinine Clearance (mL/min)	Ixazomib dose	Lenalidomide dose
≥ 60	No dose adjustment	No dose adjustment
30 – <60	No dose adjustment	10 mg daily*
< 30 (not requiring dialysis)	3 mg	15 mg every other day
< 30 (requiring dialysis)	3 mg**	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.

***Ixazomib is not dialyzable and can be administered without regard to the timing of dialysis.

Dosage in the Elderly

No dosage adjustment of ixazomib is required for patients over 65 years of age. No clinically significant differences in safety and efficacy have been demonstrated.

The incidences of serious and non-serious adverse events with lenalidomide are significantly higher in patients > 65 years (constipation, confusion, dyspnea, atrial fibrillation, diarrhea, fatigue, pulmonary embolism, syncope). This may be related to renal impairment. Monitor geriatric patients closely, especially cardiac and renal function. Consider dose modification based on degree of renal impairment.

Dosage based on ethnicity:

No clinically significant effect demonstrated during PK analysis of ixazomib; mean AUC was 35% higher in Asian patients than White patients.

Children:

Safety and efficacy of both ixazomib and lenalidomide has not been established.

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F - Adverse Effects

Refer to ixazomib, 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 • Peripheral neuropathy • Edema • Headache • Cough, dyspnea • Eye disorders • Nausea, vomiting (generally mild)	• Dizziness • Rash, pruritus (may be severe) • Tremor • Infection • Anorexia • Dyspepsia • Hyperglycemia • Abnormal electrolytes • Dysguesia • Depression • Insomnia • Abdominal pain	• Venous and arterial thromboembolism • Cholecystitis • Pneumonitis • Renal failure • ↑ LFTs • Adrenal insufficiency • Cardiotoxicity • Arrhythmia • Hypersensitivity • GI ulcer • Hemolysis • Muscle weakness • Myelitis • Pancreatitis • PRES • Thrombotic thrombocytopenic purpura • Tumor lysis syndrome • Wound dehiscence

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G - Interactions

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

- Avoid strong CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc.) as they reduce ixazomib concentrations
- Avoid taking ixaxomib with high-fat meals due to decreased abosorption
- Digoxin levels may increase if taken together with lenalidomide; caution and monitor levels
- Additive risks of thromboembolic events with lenalidomide and hormonal therapies, erythropoietic agents, corticosteroids; monitor carefully and consider anticoagulant prophylaxis

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H - Drug Administration and Special Precautions

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

Administration

Ixazomib:

- Ixazomib should be taken once a week on the same day and at approximately the same time for the first 3 weeks of a four week cycle.
- The capsule should be swallowed whole with water, on an empty stomach (at least one hour before or at least two hours after food).
- The capsule should not be crushed, chewed, or opened. Direct contact with capsule contents should be avoided as inhalation, ingestion, or skin absorption may be harmful.
- If a dose is missed, it should be taken only if the next scheduled dose is ≥ 72 hours away. A double dose should not be taken to make up for a missed dose.
- If a patient vomits after taking a dose, the patient should not repeat the dose; resume dosing at the time of the next scheduled dose.
- Store capsules at room temperature (15-30^{o}C) in original packaging. Do not freeze.

Lenalidomide:

- 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)

Dexamethasone:

- oral self-administration
- give tablets with food, preferably in the morning

Contraindications:

- patients who have a hypersensitivity to these drugs or any of their components
- women at risk of being pregnant and male patients who do not comply with contraception requirements

Other Warnings/Precautions:

- Avoid direct contact with capsule contents; ixazomib may be harmful by inhalation, ingestion, or skin absorption.
- 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 lenalidomide is 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.

Pregnancy and Lactation:

Lenalidomide is contraindicated in pregnancy and in females and males of childbearing potential who do not comply with the contraception conditions of the RevAid® program. Females of childbearing potential (all women who are not ≥ 2 years menopausal OR have not had hysterectomy or bilateral oophorectomy) must be capable of understanding and complying with the patient registration, education, and safety requirements of the RevAid® program, regular pregnancy testing and the use of two simultaneous contraception methods (must be started at least one month prior to starting treatment, continued during dose interruptions, during treatment and for at least 1 month following the cessation of lenalidomide). SEE FULL DETAILS ON THE REVAID® PROGRAM. Hormonal contraceptives are not recommended due to the increased risk of thromboembolism. If pregnancy occurs during treatment, lenalidomide must be discontinued and patient referred to a gynecologist/obstetrician for evaluation and counselling.

Lenalidomide is present in semen, and there is a potential risk of birth defects, stillbirths and spontaneous abortions in the exposed fetus, Male patients must be capable of understanding and

complying with the patient registration, education, and safety requirements of the RevAid®, including mandatory contraceptive measures for men (condoms should be used even with vasectomized males) and must inform their female sexual partners of the risk. Male patients should not donate semen while taking lenalidomide and for 4 weeks after cessation.

Patients should not donate blood while taking lenalidomide and for 4 weeks after stopping therapy to prevent fetal exposure via transfusion of pregnant women.

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 every 2 weeks for the first 12 weeks, then before each cycle
- Clinical assessments and grading of cardiac and respiratory symptoms, rash, fatigue, infection, bleeding, tumour lysis syndrome, neuropathy, GI effects, edema, pain, eye problems, arterial and venous thromboembolism; At each visit
- Liver function tests; Baseline and before each cycle
- Renal function tests; Baseline and before each cycle
- RevAid requirements regarding pregnancy tests for women of child-bearing potential; Before starting and as indicated per RevAid
- Thyroid function tests; Baseline and as clinically indicated
- Cancer screening for occurrence of second primary malignancy; Assess risk prior to starting treatment; then at each visit or as clinically indicated

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

Suggested Clinical Monitoring

- ECG; Baseline and as clinically indicated
- INR in patients receiving warfarin; Baseline and as clinically indicated

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Ixazomib and lenalidomide drug monographs, Cancer Care Ontario.

Ninlaro (ixazomib) product monograph. Takeda Canada Inc. August 3, 2016.

Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016; 374:1621-1634.

PEBC Advice Documents or Guidelines

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

May 2019 Updated emetic risk category; added PEBC guideline link

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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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