Regimen Monograph

A - Regimen Name

BORTDEXALENA Regimen

Bortezomib-Dexamethasone-Lenalidomide

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 patients with previously untreated multiple myeloma, who have good performance status

(Note: Patients who do not meet the LU eligibility criteria for lenalidomide may apply for case-by-case consideration through the EAP.)

Supplementary Public Funding

bortezomib
New Drug Funding Program (Bortezomib - In Combination with Lenalidomide and Dexamethasone for Previously Untreated Multiple Myeloma Pre-SCT) (NDFP Website)

bortezomib
New Drug Funding Program (Bortezomib - In Combination with Lenalidomide and Dexamethasone for Previously Untreated Multiple Myeloma Without Intent for Stem Cell Transplantation) (NDFP Website)

lenalidomide
ODB Limited Use (lenalidomide - Induction therapy for transplant eligible, newly diagnosed multiple myeloma, according to clinical criteria) (ODB Formulary)

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

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

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B - Drug Regimen

bortezomib	1.3 to 1.5 mg /m²	IV / Subcut	Days 1, 8, 15

Alternative schedule:
bortezomib 1.3 mg/m^2 IV / Subcut on Days 1, 4, 8, 11

lenalidomide	10 to 25 mg	PO	Days 1 to 14
dexamethasone	40* mg	PO	Days 1, 8 and 15

*In elderly patients, the dexamethasone dose should be reduced (i.e. to 20 mg once weekly).

Note: Different doses and/or dosing schedules have been used in clinical trials. Careful consideration of risk vs. benefit, the published literature and the protocol being used is required prior to finalizing the doses to be used for individual patients.

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.

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Transplant ineligible patients:

For up to 8 cycles unless disease progression or unacceptable toxicity occurs

Starting with cycle 9 onwards, continue with lenalidomide (at dose tolerated at the end of cycle 8) and dexamethasone (DEXALENA*) as maintenance until disease progression or unacceptable toxicity.

(*Refer to schedule in Durie et al)

Transplant eligible patients:

Give up to 4 cycles and assess for response and suitability for transplant.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low
No routine prophylaxis for lenalidomide

- Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Other Supportive Care:

- Antiviral prophylaxis for herpes zoster is recommended.
- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.
- 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.

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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.

Dosage with toxicity

Dose levels

Dose level	Bortezomib (mg/m^2)	Lenalidomide (mg)	Dexamethasone (mg)
0	1.3	25	40
-1	1	15	20
-2	0.7	10	12
-3	Discontinue if further reduction indicated	5	Discontinue if further reduction indicated
-4	Not applicable	Discontinue	Not applicable

Hematologic toxicity*

Toxicity during cycle (counts x 10^9/L)	Bortezomib**	Lenalidomide**
1st instance: platelets < 30	Consider hold until platelets ≥ 30, then resume at 1 dose level reduction	Hold until platelets ≥ 30, then resume at 1 dose level reduction

Subsequent instances: platelets < 30	Consider hold until platelets ≥ 30, then resume at 1 dose level reduction	Hold until platelets ≥ 30, then resume at 1 additional dose level reduction
1st instance: ANC < 0.75	Hold until ANC ≥ 1, then resume at the same dose	Hold until ANC ≥ 1, add G-CSF if possible, then resume at the same dose if isolated neutropenia. Reduce dose by 1 dose level if other toxicity.
Subsequent instances: ANC < 0.75	Hold until ANC ≥ 1, then resume at 1 dose level reduction	Hold until ANC ≥ 1, add G-CSF if possible, then resume at 1 dose level reduction

*no dosage adjustment required for dexamethasone
**do not start a new cycle until ANC ≥ 1 and platelets ≥ 70

Non-hematologic toxicity

Toxicity	**Bortezomib**	**Lenalidomide**	**Dexamethasone**
Grade 2 fluid retention	Reduce one dose level	n/a	Consider dose reduction
Grade 3 or 4 fluid retention	Discontinue	n/a	Consider dose reduction
Grade 2 to 3 rash	For drug related grade 3: Hold until ≤ grade 1 or baseline, then resume at 1 dose level reduction. If recurs, reduce an additional dose level	Hold or consider discontinuing	N/A
Angioedema, anaphylaxis, OR Grade 4 skin rash OR Exfoliative or bullous rash, OR Suspected Stevens Johnson Syndrome, Toxic epidermal necrolysis or DRESS	Discontinue		

Pneumonitis	Hold and investigate; discontinue if confirmed.		n/a
PRES / PML	Hold and investigate; discontinue if confirmed.		
Increased LFTs	n/a	Hold until ≤ baseline. Consider restarting at a lower dose.	n/a
Solid organ transplant rejection	Discontinue		
Any ≤ grade 3 non-heme toxicity (for neurotoxicity with bortezomib, see separate table below)	Hold until ≤ grade 1 or baseline, then resume at 1 dose level reduction. If recurs, reduce an additional dose level. For grade 4 toxicity, consider discontinuation.	Hold until ≤ grade 1 or baseline, then resume at 1 dose level reduction. If recurs, reduce an additional dose level.	Hold until ≤ grade 1 or baseline, then resume at 1 dose level reduction. If recurs, reduce an additional dose level.

Dosage for neurotoxicity

Patients with pre-existing severe neuropathy should be treated with bortezomib only after careful risk vs. benefit assessment.

Severity of Neuropathy	**Bortezomib dosage**
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	No change
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce 1 dose level
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Hold until toxicity resolves. Upon recovery, resume at 1 additional dose level reduction and give once weekly.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life-threatening or leads to paralysis) and/or severe autonomic neuropathy	Discontinue permanently

Hepatic Impairment

Bortezomib is metabolized by liver enzymes and exposure is increased in patients with moderate to severe hepatic impairment.

Bilirubin		AST	Bortezomib starting dose	Lenalidomide starting dose	Dexamethasone starting dose
≤ 1 x ULN	and	> ULN	No change	No change	No change
> 1 – 1.5 x ULN	and	Any	No change	No change	No change
> 1.5 x ULN	and	Any	1st cycle: ↓ to 0.7 mg/m^2 Subsequent cycles: Consider ↑ dose to 1 mg/m^2 OR further ↓ dose to 0.5 mg/m^2 based on patient tolerability	No data	No change

Renal Impairment

Lenalidomide clearance is decreased while exposure is increased in renal impairment.

Creatinine Clearance (mL/min)	Lenalidomide Starting Dose	Bortezomib starting dose	Dexamethasone starting dose
30 to < 60	10 mg daily*	No change	No change
< 30 (not requiring dialysis)	15 mg every other day	No change; monitor carefully	No change
< 30 (requiring dialysis)	No phase III clinical trial experience in this setting. 5 mg once daily. On dialysis days, administer following dialysis	No change. On dialysis days, administer following dialysis	No change

* may be escalated to 15 mg q24h after 2 cycles if patient is not responding to treatment and is tolerating the drug.

Dosage in the Elderly

The incidences of serious and non-serious adverse events are significantly higher in patients > 65 years with lenalidomide and this may be related to renal impairment. Monitor elderly patients closely, especially cardiac and renal function. Dose modification based on degree of renal impairment is required.

No dosage adjustment is required for bortezomib or dexamethasone.

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F - Adverse Effects

Refer to bortezomib, 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 • Diarrhea • Nausea, vomiting	• Constipation (may be severe) • Neuropathy (may be severe) • Myelosuppression +/- infection (including opportunistic, viral reactivation), bleeding (may be severe) • Anorexia, weight loss • Musculoskeletal pain • Edema • Headache • Cough, dyspnea	• Dizziness • Rash (may be severe; SJS, TEN, DRESS) • Tremor • Insomnia • Blurred vision • Dyspepsia, abdominal pain • Hyperglycemia • Abnormal electrolytes • Dysgeusia • Depression • Hypotension • Steroid effects	• Arrhythmia • Increased QTc interval • Arterial / venous thromboembolism • Cardiotoxicity • Pulmonary hypertension • Tumour lysis syndrome • Hypersensitivity • Hemolytic uremic syndrome • Hemolysis • Disseminated intravascular coagulation • GI obstruction / perforation • Pancreatitis

			• Pneumonitis • Hepatotoxicity, cholecystitis • Rhabdomyolysis • Nephrotoxicity • Adrenal insufficiency • PRES / PML • Seizure • Secondary malignancy • Graft loss (in stem cell transplant patients) • Hyper/ hypothyroidism • GVHD • Solid organ transplant rejection

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G - Interactions

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

- Avoid bortezomib co-administration with strong CYP3A4 inhibitors and inducers.
- Avoid use of bortezomib with high dose cytarabine or daunorubicin given increased risk of ARDS.
- Avoid green tea and preparations containing green tea during bortezomib treatment .
- Avoid vitamin C supplementation during bortezomib treatment.
- Caution and monitor with drugs associated with neuropathy, hypoglycemia and hypotension.
- Caution and consider non-hormonal method(s) of contraception; use of oral contraceptives or other hormonal methods of contraception may increase the risk of blood clots.
- Lenalidomide increases the concentration of digoxin. Use caution and monitor digoxin levels.
- Lenalidomide increases the risk of thromboembolism, and can have an additive effect with hormonal therapy, erythropoietic agents, and corticosteroids.

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H - Drug Administration and Special Precautions

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

Administration

Bortezomib:

- Bortezomib should be administered via intravenous or subcutaneous routes only.
- Bortezomib is fatal if given intrathecally.
- Bortezomib has a narrow therapeutic range. If a different reconstituted concentration is used for each route of administration, exercise caution when reconstituting and calculating the dose volume.
- The Canadian product monograph recommends the following concentrations to be used for injections: ► Intravenous: 1 mg/mL; ► Subcutaneous: 2.5 mg/mL
- If local injection site reactions occur following subcutaneous bortezomib, consider using a less concentrated solution subcutaneously (1 mg/mL), or administer as IV.
- IV: Administered as a 3 to 5 second IV push through a peripheral or central IV catheter, followed by a standard saline flush; no central line is required.
- For subcutaneous use, bortezomib solution is injected into the right or left sides of the thighs or abdomen. Rotate injection sites with subsequent injections. Give new injections at least 2.5 cm from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.

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).

Dexamethasone:

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

Contraindications

- Patients with hypersensitivity to bortezomib, boron, mannitol, lenalidomide, pomalidomide, thalidomide or any ingredient in the formulation
- Bortezomib is NOT for intrathecal use
- Pregnant and breastfeeding women
- Women at risk of being pregnant and male patients who do not comply with contraception requirements (see Pregnancy section in lenalidomide drug monograph for additional details)

Other 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.
- Caution should be exercised when driving or using machinery, and in patients on medication(s) that may lead to hypotension, or patients with dehydration or history of syncope, due to the risk of hypotension and dizziness.
- Use with caution in patients with amyloidosis, those with risk factors for seizures, cardiac disease, pre-existing neuropathies

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.
- Bortezomib is not recommended for use during pregnancy.
- 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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; baseline and before each cycle
- Blood glucose levels, especially in patients using antidiabetic medications; baseline, before each cycle and as clinically indicated
- Liver and renal function tests; Baseline and before each cycle
- CXR; baseline, then CXR and lung function assessment if ILD is suspected
- Thyroid function tests; Baseline and as clinically indicated
- Specific to lenalidomide: Pregnancy testing requirements for women of child-bearing potential; prior to starting treatment and as indicated
- Cancer screening for occurrence of second primary malignancy; assess risk prior to starting treatment, then at each visit or as clinically indicated
- Clinical toxicity ratings of fatigue, neurotoxicity, infection (including viral reactivation), bleeding, rash, diarrhea, constipation, arterial and venous thromboembolism, respiratory symptoms, tumour lysis syndrome, cardiovascular and GI side effects, 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

- EKG at baseline; repeat if arrhythmia suspected
- LVEF monitoring in patients with cardiac risk factors; baseline and as clinically indicated
- INR in patients receiving warfarin; baseline and regular

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J - Administrative Information

Outpatient prescription for home administration (lenalidomide & dexamethasone)

Approximate Patient Visit	0.5 hour
Pharmacy Workload (average time per visit)	16.369 minutes
Nursing Workload (average time per visit)	27.5 minutes

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K - References

Attal M, Lauwers-Cances V, Hulin C, et al, Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. N Engl J Med 2017;376(14):1311-20.

Bortezomib drug monograph. Ontario Health (Cancer Care Ontario).

Durie BGM, Hoering A, Sexton R, et al, Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). Blood Cancer J 2020;10(5):53.

Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet 2017 Feb 4;389(10068):519-27.

Lenalidomide drug monograph. Ontario Health (Cancer Care Ontario).

Richardson PG, Xie W, Jagannath S, et al. A phase 2 trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory myeloma. Blood 2014 Mar 6;123(10):1461-9.

Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood 2010 Aug 5;116(5):679-86.

PEBC Advice Documents or Guidelines

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

December 2023 Modified Supplementary public funding and Drug regimen sections

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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.

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