

## Regimen Monograph

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## A - Regimen Name

**CYBORD Regimen**

**Cyclophosphamide-Bortezomib-Dexamethasone** (in patients eligible for ASCT)

**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** Induction therapy for patients with previously untreated multiple myeloma, prior to autologous stem cell transplantation (ASCT).

This regimen may also be used for light-chain amyloidosis.

**Supplementary Public Funding** [cyclophosphamide](#)  
ODB - General Benefit (cyclophosphamide - oral tablets) ([ODB Formulary](#) )

[bortezomib](#)  
New Drug Funding Program (Bortezomib - Previously Untreated - Multiple Myeloma Pre-Stem Cell Transplant) ([NDFP Website](#))

**dexamethasone**  
ODB - General Benefit (dexamethasone) ([ODB Formulary](#) )

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<a href="#">cyclophosphamide</a> <sup>†</sup>	300 mg /m <sup>2</sup>	PO	Days 1, 8, 15, 22
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(Outpatient prescription; available as 25 mg or 50 mg tablets)

† Missed doses should not be made up.

<a href="#">bortezomib</a> *	1.5 mg /m <sup>2</sup>	IV / Subcut	Days 1, 8, 15, 22
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\* Missed doses should not be made up, and there should be a minimum of 72 h between bortezomib doses.

**Cycles 1 and 2:**

<a href="#">dexamethasone</a> <sup>^</sup>	40 mg	PO	Daily on days 1 to 4, 9 to 12, 17 to 20
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(outpatient prescription in 4 mg tablets)

**Cycles 3 and beyond:**

<a href="#">dexamethasone</a> <sup>^</sup>	40 mg	PO	Once weekly (on days 1, 8, 15, 22)
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<sup>^</sup>The dexamethasone dose should be reduced in elderly patients.

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unless disease progression or unacceptable toxicities. Assess at the end of 4 cycles for response and suitability for transplant.

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## D - Premedication and Supportive Measures

**Antiemetic Regimen:** Low  
Consider prophylaxis daily for cyclophosphamide PO

### Other Supportive Care:

- Oral hydration is encouraged to prevent dose-related hemorrhagic cystitis.
- Consider prophylaxis for herpes zoster
- Prophylaxis with a proton pump inhibitor and an antibiotic (e.g. quinolone) were also used in clinical trials.
- Use of anti-fungal mouthwash was recommended in the clinical trial.
- Consider prophylaxis for tumour lysis syndrome in high risk patients (e.g. plasma cell leukemia).

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

### Suggested dose levels

Dose level	Cyclophosphamide (mg/m <sup>2</sup> )	Bortezomib (mg/m <sup>2</sup> )	Dexamethasone (mg) cycles 1 and 2	Dexamethasone (mg) cycles 3 and onwards
-1	300 days 1, 8, 15	1.3 days 1, 8, 15, 22	20 days 1-4, 9-12, 17-20	20 days 1, 8, 15, 22
-2	300 days 1 and 8	1 days 1, 8, 15, 22	20 days 1-4	20 days 1, 8, 15
-3	300 day 1	0.7 days 1, 8, 15, 22	10 days 1-4	10 days 1, 8, 15
-4	Discontinue	Discontinue	Discontinue	Discontinue

Exercise clinical discretion in patients with low counts due to bone marrow infiltration of myeloma.

Full dosing of drugs should be considered and patients to be monitored closely for the first 2 cycles.

### **Hematologic Toxicities (Table A)**

<b>Cycle</b>	<b>Toxicity / Counts (x 10<sup>9</sup>/L)</b>	<b>Bortezomib</b>	<b>Cyclophosphamide</b>	<b>Dexamethasone</b>
Day one of Cycle	Platelets < 50 and/or ANC < 1 on day 1 of cycle	Hold until recovery*; ↓ by 1 dose level for next dose/cycle	Hold until recovery*; then ↓ by 1 dose level (if occurs on day 15, omit for rest of cycle then ↓ 1 dose level)	No change. For day 1, delay until start of bortezomib and cyclophosphamide.
During Cycle	Grade 4 neutropenia, or febrile neutropenia or grade 3 neutropenia ≥ 7 days <sup>#</sup>	Day 1: Hold until recovery* then ↓ by 1 dose level  Other days: Omit for rest of cycle AND ↓ 1 dose level for next cycle		
During Cycle	platelets < 50 or thrombocytopenic bleeding <sup>#</sup>	Hold until recovery* then ↓ by 1 dose level		

\*Restart treatment if platelets ≥ 50 x 10<sup>9</sup>/L, ANC ≥ 1 x 10<sup>9</sup>/L, toxicities recovered to ≤ grade 2 (or as defined in table B).

<sup>#</sup> since last dose – for example if day 1, would be since last cycle; or if on D8, would be since day 1

### **Non-Hematologic Toxicities (Table B)**

<b>Toxicity</b>	<b>Dose modification and delay</b>
Grade 1 or 2 hemorrhagic cystitis	↓ cyclophosphamide by 1 dose level
Grade 3 or 4 hemorrhagic cystitis	Discontinue cyclophosphamide
Grade 3 related non-hematologic toxicity (see table C for neurotoxicity)	Hold suspect drugs until ≤ grade 1/baseline then restart with 1 dose level ↓
Grade 4 related non-hematologic or any grade RPLS/ PML/ pneumonitis <sup>^</sup>	Discontinue all drugs
Severe corticosteroid related toxicity (e.g. GI, hyperglycemia, confusion, mood changes or muscle weakness interfering with activities of daily living)	↓ dexamethasone by 1 dose level

\*Restart treatment if platelets  $\geq 50 \times 10^9/L$ , ANC  $\geq 1 \times 10^9/L$ , toxicities recovered to  $\leq$  grade 2 (or as defined in table B). If treatment held for  $> 2$  weeks, discontinue.

^Patients with symptoms of pneumonitis/ARDS should have all drugs held, be appropriately investigated and managed; if diagnosis is confirmed, permanently discontinue.

### **Dosage for Neurotoxicity (Table C)**

Patients with pre-existing severe neuropathy should be treated with bortezomib only after careful risk/benefit assessment. Dose reductions are not required for cyclophosphamide or dexamethasone.

<b>Severity of Peripheral Neuropathy</b>	<b>Bortezomib Dosage Modification</b>
Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	↓ 1 dose level
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Hold bortezomib until $\leq$ grade 1, then ↓ 1 further dose level than above
Grade 4 OR RPLS (sensory neuropathy which is disabling or motor neuropathy that is life-threatening or leads to paralysis)	Discontinue

### **Hepatic Impairment**

No dosage adjustment required for dexamethasone.

Bortezomib is metabolized by liver enzymes and exposure is increased in patients with moderate to severe hepatic impairment. Patients with hepatic impairment should be treated with extreme caution, should be closely monitored for toxicities, and dose reduction should be considered.

<b>Bilirubin</b>	<b>AST</b>	<b>Bortezomib Starting Dose (mg/m<sup>2</sup>)</b>	<b>Cyclophosphamide Dose</b>
$\leq 1 \times$ ULN	$>$ ULN	No change	No change
$> 1 - 1.5$ $\times$ ULN	Any	No change	No change
$> 1.5 - 3$	Any	First cycle: ↓ to 0.7	Caution

x ULN		Subsequent cycles: Consider ↑ dose to 1 or further ↓ dose to 0.5 based on patient tolerability	
> 3 x ULN	Any		

### **Renal Impairment**

No dosage adjustment required for dexamethasone.

<b>Creatinine Clearance (mL/min)</b>	<b>Cyclophosphamide (% previous dose)</b>	<b>Bortezomib (% previous dose)</b>
>60	No change	No change
>30-60	No change	No change
10-30	50% to 75%	No change (monitor carefully)
<10	50% or omit	No change (monitor carefully)

\*may escalate dose as creatinine clearance improves

### **Dosage in the Elderly**

No dose modification routinely required for cyclophosphamide, but should be used with caution. There is no evidence to suggest that bortezomib dosage adjustments are necessary in elderly patients.

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## **F - Adverse Effects**

Refer to [cyclophosphamide](#), [bortezomib](#), dexamethasone drug monograph(s) for additional details of adverse effects.

<b>Very common (≥ 50%)</b>	<b>Common (25-49%)</b>	<b>Less common (10-24%)</b>	<b>Uncommon (&lt; 10%), but may be severe or life-threatening</b>
<ul style="list-style-type: none"> <li>• Fatigue</li> </ul>	<ul style="list-style-type: none"> <li>• Constipation (may</li> </ul>	<ul style="list-style-type: none"> <li>• Musculoskeletal</li> </ul>	<ul style="list-style-type: none"> <li>• Arterial / venous</li> </ul>

<ul style="list-style-type: none"> <li>• Diarrhea</li> <li>• Nausea, vomiting</li> <li>• Alopecia</li> <li>• Steroid effects (weight gain, myopathy, cataracts, hyperglycemia, gastric irritation, mood changes)</li> </ul>	<ul style="list-style-type: none"> <li>• be severe)</li> <li>• Neuropathy (may be severe)</li> <li>• Anorexia, weight loss</li> <li>• Headache</li> <li>• Myelosuppression ± bleeding, infection (including atypical, may be severe)</li> <li>• Cough, dyspnea (may be severe)</li> </ul>	<ul style="list-style-type: none"> <li>• pain</li> <li>• Rash (may be severe)</li> <li>• Insomnia</li> <li>• Edema</li> <li>• Abdominal pain</li> <li>• Dizziness</li> <li>• Cystitis (may be severe)</li> <li>• Hypotension</li> </ul>	<ul style="list-style-type: none"> <li>• thromboembolism</li> <li>• Tumour lysis syndrome</li> <li>• Disseminated intravascular coagulation</li> <li>• Renal failure</li> <li>• RPLS, PML</li> <li>• GI obstruction / perforation</li> <li>• Pancreatitis</li> <li>• ↑ LFTs</li> <li>• Hypersensitivity</li> <li>• Seizure</li> <li>• Cardiotoxicity</li> <li>• ↑ QTc, arrhythmia</li> <li>• Secondary malignancies</li> <li>• SIADH</li> <li>• Vasculitis</li> <li>• Hemolytic uremic syndrome</li> <li>• PRES</li> <li>• Pericarditis</li> <li>• Pulmonary hypertension</li> <li>• Nephrotic syndrome</li> <li>• Sudden death</li> </ul>
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## G - Interactions

Refer to [cyclophosphamide](#), [bortezomib](#), dexamethasone drug monograph(s) for additional details

- Exercise caution and monitor blood glucose when co-administered with hypoglycemic agents
- Avoid co-administration with strong CYP3A4 inhibitors and inducers. If co-administered with CYP3A4 inhibitors, monitor closely for toxicity. Avoid grapefruit juice 48 hours before and on the day of receiving cyclophosphamide.
- Caution and monitor with drugs associated with neuropathy, hypotension, cardiotoxicity, nephrotoxicity, hepatotoxicity, pulmonary toxicity, thromboembolism (additive effects)

- Avoid green tea and preparations containing green tea during bortezomib treatment given potential for reduced efficacy.
- Avoid vitamin C supplementation during bortezomib treatment given potential for reduced efficacy. If must give, suggest vitamin C up to 500 mg given 12 hours before or after bortezomib dose.
- Use with caution with allopurinol, thiazide diuretics and ACE inhibitors as increased myelosuppression with cyclophosphamide has been reported.
- Avoid concomitant use of cyclophosphamide and lovastatin, as increased rhabdomyolysis has been reported.
- Prolonged post-operative apnea may occur with depolarizing muscle relaxants (e.g. succinylcholine). Notify anesthesiologist prior to use; succinylcholine dose modification may be required.
- Cyclophosphamide may decrease absorption of digoxin and verapamil; monitor for reduced drug effects

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## H - Drug Administration and Special Precautions

Refer to [cyclophosphamide](#), [bortezomib](#), dexamethasone drug monograph(s) for additional details

### **Administration**

#### **Cyclophosphamide:**

- Oral hydration is strongly encouraged; for PO cyclophosphamide: 8-10 (8oz) glasses of fluid per day. Inadequate total hydration may result in dose-related hemorrhagic cystitis. Patients should be encouraged to empty their bladder frequently to minimize dwell times.
- Oral tablets should be administered as a single dose in the morning, with or without food.
- Store in the original packaging at room temperature, away from heat, light or moisture.

#### **Bortezomib:**

- Bortezomib should be administered via intravenous or subcutaneous routes only.



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- 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.
  - Some centres have routinely used the bortezomib 1mg/mL concentration for all subcutaneous injections.
  - 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.

**Dexamethasone:**

- Oral self-administration.
- Give tablets with food, preferably in the morning.

**Contraindications**

- Patients with severe hepatic or renal impairment.
- Patients with severe myelosuppression and/or immunosuppression.
- Patients who have a hypersensitivity to bortezomib or cyclophosphamide or any of its components.
- Patients with active infection, particularly varicella zoster infection.

**Warnings/Precautions**

- Patients with urinary outflow obstruction.
- Patients with adrenal insufficiency.

- In combination with neuromuscular blockers.
- Avoid live or live-attenuated vaccines as use may result in serious or fatal infections in immunocompromised patients. Reduced immunogenicity may occur with use of inactivated vaccines.
- 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 or risk factors for seizures.
- Use with caution in patients with risk factors for or existing cardiac disease.
- Use with caution in patients with pre-existing peripheral or autonomic neuropathy.

### **Pregnancy/lactation**

- Cyclophosphamide is **mutagenic, carcinogenic, genotoxic, teratogenic** and **fetotoxic** in humans. Testicular atrophy and sterility may occur in males. Sperm-banking before treatment should be considered. Amenorrhea and ovarian failure may occur in females. Gonadal dysfunction may reverse with time, but future reproductive capacity is uncertain.
- Women of childbearing potential should avoid becoming pregnant while being treated with bortezomib. Adequate contraception should be used by both genders during bortezomib treatment and for **3 months** after treatment completion.
- Breastfeeding is not recommended.

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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**

- Blood glucose levels, especially in patients using antidiabetic medications; baseline and regular
- CBC; baseline and at each visit

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- CXR; baseline, then CXR and lung function assessment if ILD is suspected;
  - Liver and renal function tests, electrolytes; baseline and regular
  - Routine clinical assessment of fatigue, neurotoxicity, infection, bleeding, hypotension, cystitis, thromboembolism, respiratory symptoms, tumour lysis syndrome, cardiovascular and GI side effects
  - Grade toxicity using the current [NCI-CTCAE \(Common Terminology Criteria for Adverse Events\) version](#)

#### Suggested Clinical Monitoring

- Urinalysis; baseline and regular
- LVEF monitoring in patients with cardiac risk factors; baseline and as clinically indicated

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### **J - Administrative Information**

Cyclophosphamide and Dexamethasone: Outpatient prescription for home administration

Approximate Patient Visit	0.5 hour
Pharmacy Workload (average time per visit)	16.369 minutes
Nursing Workload (average time per visit)	27.500 minutes

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### **K - References**

Bortezomib and cyclophosphamide drug monographs, Cancer Care Ontario.

Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. *Leukemia* 2009; 23: 1337–41.

Reeder CB, Reece DE, Kukreti V, et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. *Blood* 2010; 115(16): 3416-7.

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**PEBC Advice Documents or Guidelines**

- [Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline](#)

**September 2019** Added note on dexamethasone dose in the elderly

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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.*

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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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