

Regimen Monograph

[Regimen Name](#) | [Drug Regimen](#) | [Cycle Frequency](#) | [Premedication and Supportive Measures](#) | [Dose Modifications](#) | [Adverse Effects](#) | [Interactions](#) | [Drug Administration and Special Precautions](#) | [Recommended Clinical Monitoring](#) | [Administrative Information](#) | [References](#) | [Other Notes](#) | [Disclaimer](#)

A - Regimen Name

CYBORP Regimen

Cyclophosphamide-Bortezomib-Prednisone

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 Treatment of relapsed/refractory multiple myeloma

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

[bortezomib](#)
New Drug Funding Program (Bortezomib - Relapsed or Refractory Multiple Myeloma) ([NDFP Website](#))

prednisone
ODB - General Benefit (prednisone) ([ODB Formulary](#))

[back to top](#)

B - Drug Regimen

[cyclophosphamide](#)† 300 mg /m² PO Days 1, 8, 15, 22

(Outpatient prescription; available as 25 mg or 50 mg tablets)

† Missed doses should not be made up.

[bortezomib](#)* 1.5 mg /m² IV / Subcut Days 1, 8, 15

(Prior authorization is required for PDRP funding of this drug within this regimen)

* Missed doses should not be made up, and there should be a minimum of 72 h between bortezomib doses.

prednisone 100 mg PO Every 2 days

(outpatient prescription; available as 5mg and 50mg tablets)

[back to top](#)

C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

[back to top](#)

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.
- Strongly consider antiviral prophylaxis for herpes zoster
- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely

Also refer to [CCO Antiemetic Recommendations](#).

[back to top](#)

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	Bortezomib (Days 1, 8, 15)	Prednisone
-1	300 mg/m ² days 1, 8, 15	1.3 mg/m ²	50 mg
-2	300 mg/m ² days 1 and 8	1 mg/m ²	Physician's discretion
-3	300 mg/m ² day 1	0.7 mg/m ²	Physician's discretion
-4	Discontinue	Discontinue	Discontinue

Hematologic toxicities (Table A):

Cycle	Toxicity / Counts (x 10 ⁹ /L)	Bortezomib	Cyclophosphamide	Prednisone
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 [#]	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	Hold until		

	thrombocytopenic bleeding [#]	recovery* then ↓ 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).

[#] 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):

Toxicity	Dose modification and delay
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 drug(s) until \leq grade 1/baseline then restart with 1 dose level ↓
Grade 4 related non-hematologic or any grade RPLS/ PML/ pneumonitis [^]	Discontinue regimen
Severe corticosteroid related toxicity (e.g. GI, hyperglycemia, confusion, mood changes or muscle weakness interfering with activities of daily living)	↓ prednisone 1 dose level

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

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 prednisone.

Dosage for Neurotoxicity (Table C)

Severity of Peripheral Neuropathy	Bortezomib Dose Modification
Grade 1 (paresthesias, weakness 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	Hold bortezomib until \leq grade 1, then ↓ 1 further

with activities of daily living)	dose level than above
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life-threatening or leads to paralysis)	Discontinue

Hepatic Impairment

No dosage adjustment required for prednisone.

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.

Bilirubin	AST	Bortezomib Dose	Cyclophosphamide Dose
≤ 1 x ULN	> ULN	No change	No change
> 1 – 1.5 x ULN	Any	No change	No change
> 1.5 – 3 x ULN	Any	First cycle: ↓ to 0.7mg/m ² Subsequent cycles: Consider ↑ dose to 1mg/m ² or further ↓ dose to 0.5mg/m ² based on patient tolerability.	Caution

Renal Impairment

No dosage adjustment required for prednisone.

Creatinine Clearance (mL/min)	cyclophosphamide (% previous dose)	bortezomib (% previous dose)
>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)
-----	-------------	-------------------------------

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.

[back to top](#)

F - Adverse Effects

Refer to [cyclophosphamide](#), [bortezomib](#), 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
<ul style="list-style-type: none"> • Fatigue • Diarrhea • Nausea, vomiting • Alopecia • Steroid effects (weight gain, myopathy, cataracts, hyperglycemia, gastric irritation, mood changes) 	<ul style="list-style-type: none"> • Constipation (may be severe) • Neuropathy (may be severe) • Anorexia, weight loss • Headache • Myelosuppression ± bleeding, infection (including atypical, may be severe) • Cough, dyspnea (may be severe) 	<ul style="list-style-type: none"> • Musculoskeletal pain • Rash (may be severe) • Insomnia • Edema • Abdominal pain • Dizziness • Cystitis (may be severe) • Hypotension 	<ul style="list-style-type: none"> • Arterial thromboembolism • Venous thromboembolism • Tumour lysis syndrome • Disseminated intravascular coagulation • Renal failure • RPLS, PML • GI obstruction • GI perforation • Pancreatitis • ↑ LFTs • Hypersensitivity • Seizure • Cardiotoxicity

			<ul style="list-style-type: none"> • ↑ QTc, arrhythmia • Secondary malignancies • SIADH • Vasculitis • Hemolytic uremic syndrome • PRES • Pericarditis • Pulmonary hypertension • Nephrotic syndrome • Sudden death
--	--	--	---

[back to top](#)

G - Interactions

Refer to [cyclophosphamide](#), [bortezomib](#), prednisone 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

[back to top](#)

H - Drug Administration and Special Precautions

Refer to [cyclophosphamide](#), [bortezomib](#), prednisone 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.
- 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.

Prednisone:

- 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

Other 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 and 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.

[back to top](#)

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

-
- 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

[back to top](#)

J - Administrative Information

Cyclophosphamide and Prednisone: 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

[back to top](#)

K - References

Bortezomib and cyclophosphamide drug monographs, Cancer Care Ontario

CYBORD Regimen monograph, Cancer Care Ontario.

Reece DE, Rodriguez GP, Chen C, et al. Phase I-II trial of bortezomib plus oral cyclophosphamide and prednisone in relapsed and refractory multiple myeloma. J Clin Oncol 2008;26(29):4777-83.

PEBC Advice Documents or Guidelines

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

April 2021 Added "Prior authorization is required for PDRP funding of this drug within this regimen"

to section B

[back to top](#)

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 information (for health professionals) contained in the Drug Formulary (the “Formulary”) is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

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.

While care has been taken in the preparation of the information contained in the Formulary, 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.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on

breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

[back to top](#)