Regimen Monograph

A - Regimen Name

CYCL(PO) Regimen

Cyclophosphamide (oral)

Disease Site	Hematologic - Leukemia - Chronic Lymphocytic (CLL) Hematologic - Lymphoma - Non-Hodgkin's Intermediate Grade Hematologic - Lymphoma - Non-Hodgkin's Low Grade 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.
Supplementary Public Funding	**cyclophosphamide** ODB - General Benefit (cyclophosphamide - oral tablets)

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B - Drug Regimen

Dose and frequency may vary. Two options are:

cyclophosphamide	500 mg	PO	Every 7 days

OR

cyclophosphamide	50 mg	PO	Daily

(Available as 25mg & 50mg tablets)

Can be given with or without prednisone

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate – Consider prophylaxis daily (≥ 100mg/ m2 /d)
Low – No routine prophylaxis; PRN recommended (< 100mg/ m2/ d)

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Before starting treatment:

- Exclude or correct any electrolyte imbalances
- Exclude or correct any obstructions of the urinary tract, cystitis and infections

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Dose adjustment may be needed for adrenalectomized patients.

Dose Level	Dose (mg)	
	Daily Schedule	Weekly Schedule
0	50	500
-1	25	400
-2	25 on alternate days	300

Dosage with toxicity

Toxicity (counts x 10^9/L)	**Cyclophosphamide Dose***
ANC 1 to 1.5 or platelets 75 to 100	Continue with 1 dose level reduction
ANC < 1 or platelets < 75	Hold; may consider reducing 1 dose level when restart
Grade 4 ANC or platelets, febrile neutropenia or thrombocytopenic bleeding	Hold; reduce 1 dose level
Grade 3 non-hematologic / organ	Hold; reduce 1 dose level
Grade 4 non-hematologic /organ	Discontinue
Pneumonitis	Hold, investigate and if confirmed, discontinue
Hematuria	Hold until resolution; discontinue if severe hemorrhagic cystitis
* Do not retreat until ANC > 1 x 10^9/L, platelets > 75 x 10^9/L and other toxicity recovered to ≤ grade 2.	

Hepatic Impairment

No adjustment required, but caution should be exercised especially with oral cyclophosphamide.

Bilirubin	Dose (% of previous)
1-2 x ULN	100%
>2 x ULN	Caution

Renal Impairment

Renal failure may lead to the reduced excretion of metabolites and increased toxicity. Significant falls in clearance (25-80%) with increased exposure have been documented in patients with renal impairment. Cyclophosphamide is hemodialysable and should be administered after hemodialysis.

Suggested:

Creatinine Clearance (mL/min)	Dose (% of previous)
> 50	100%
10 - 50	May consider 75%
< 10	50%; use with caution and monitor closely

Dosage in the Elderly

No dose modification routinely required, but should be used with caution.

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F - Adverse Effects

Refer to cyclophosphamide drug monograph(s) for additional details of adverse effects

More common (≥ 10%)	Less Common (1 to <10%)	Rare, and may be severe or life-threatening (Incidences <1% or unknown)
• Nausea, vomiting • Alopecia • Immunosuppression (may be severe, including opportunistic infections or reactivation) • Myelosuppression +/- infection, bleeding (may be severe)	• Cystitis • ↑ LFTs (may be severe) • Fatigue	• Arrhythmia, QT prolongation • Arterial thromboembolism • Venous thromboembolism • Cardiotoxicity • Radiation recall reaction • Delayed wound healing • Stevens-Johnson syndrome, Toxic epidermal necrolysis • VOD • Pancreatitis • Hypersensitivity • SIADH • Tumour lysis syndrome • Rhabdomyolysis • Secondary malignancy • Neurotoxicity (including central - RPLS, peripheral) • Pneumonitis • Nephrotoxicity • Bladder fibrosis

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G - Interactions

Refer to cyclophosphamide drug monograph(s) for additional details

- Avoid concomitant use with lovastatin as increased rhabdomyolysis has been reported.
- Avoid alcohol if possible, since this may increase cyclophosphamide-induced nausea and vomiting.
- Drugs which inhibit CYP3A4 (e.g. azole antifungals) and grapefruit juice may increase toxicity or decrease cyclophosphamide activation. Avoid grapefruit juice 48 hours before and on the day of receiving cyclophosphamide.
- Prolonged post-operative apnea may occur with depolarizing muscle relaxants (e.g. succinylcholine). Notify anesthesiologist prior to use; succinylcholine dose modification may be required.
- Avoid concomitant use with etanercept if possible.

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H - Drug Administration and Special Precautions

Refer to cyclophosphamide, cyclophosphamide drug monograph(s) for additional details

Administration

- Oral tablets should be administered as a single dose in the morning, with or without food.
- Hydration is recommended (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.
- Patients should avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- An oral preparation may be prepared by dissolving cyclophosphamide for injection in Aromatic Elixir USP (refer to product monograph).

Contraindications

- patients with severe hepatic or renal impairment
- patients with severe myelosuppression (leukocytes < 2.5 x 10^9/L and/or platelets < 50 x 10^9/L) and/or immunosuppression
- patients who have a hypersensitivity to this drug or any of its components
- patients with active infection, particularly *varicella zoster* infection
- patients with urinary outflow obstruction

Other Warnings/ Precautions

- Exercise caution in patients:
  - with adrenal insufficiency
  - with risk factors for cardiotoxicity or pre-existing cardiac disease
  - using cyclophosphamide in combination with neuromuscular blockers
  - with tumour infiltration in the bone marrow

- 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.
- Use caution when driving or operating machinery since cyclophosphamide may produce symptoms of vasomotor ataxia (e.g. dizziness, blurred vision, etc.)

Pregnancy/lactation

- Cyclophosphamide is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months (**for males) and at least **12 months** (for females) after the last dose.
- Breastfeeding is not recommended.
- Fertility can be affected.

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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 before each cycle
- Renal function tests; Baseline and before each cycle
- Liver function tests; Baseline and as clinically indicated
- Electrolytes; Baseline and as clinically indicated
- Urinalysis; Baseline and as clinically indicated
- Clinical toxicity assessment for gastrointestinal, cystitis, infection, bleeding, thromboembolism, cardiac or pulmonary adverse effects; At each visit

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

Suggested Clinical Monitoring

- INR; for patients on warfarin; Baseline and as clinically indicated
- ECGs; As clinically indicated
- Pulmonary function tests; As clinically indicated

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Cyclophosphamide drug monograph, Cancer Care Ontario.

Brandes LJ, Israels LG. Weekly low-dose cyclophosphamide an alternate-day prednisone: an effective low toxicity regimen for advanced myeloma. Eur J Haematol 1987;39:362-8.

Buckstein R, Kerbel RS, Shaked Y, et al. High-Dose celecoxib and metronomic ‘‘low-dose’’ cyclophosphamide is an effective and safe therapy in patients with relapsed and refractory aggressive histology non-Hodgkin’s lymphoma. Cancer Research 2006;12:5190-8.

Peterson BA, Petroni GR, Frizzera G. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukemia group B. J Clin Oncol 2003;21:5-15.

Trieu T, Trudel, S, Pond GR, et al. Weekly cyclophosphamide and alternate-day Prednisone: an effective, convenient, and well-tolerated oral treatment for relapsed multiple myeloma after autologous stem cell transplantation. Mayo Clin Proc 2005;80(12):1578-82.

Wilson K, Shelly W, Belch A et al. Weekly cyclophosphamide and alternate-day prednisone: an effective secondary therapy in multiple myeloma. Cancer Treat Rep 1987 Oct; 71(10): 981-2.

May 2019 Edited emetic risk category, adverse effects, dosage with renal impairment, administration, precaution, pregnancy/lactation, interactions and monitoring 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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