Regimen Monograph

A - Regimen Name

FC(PO) Regimen

Fludarabine (oral)-Cyclophosphamide (oral)

Disease Site	Hematologic - Leukemia - Chronic Lymphocytic (CLL)
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	Second-line treatment in patients with CLL
Supplementary Public Funding	**fludarabine** ODB Limited Use (fludarabine - For second-line therapy of patients with CLL who have failed or are intolerant to chlorambucil (tablets)) (ODB Formulary) **cyclophosphamide** ODB - General Benefit (cyclophosphamide - oral tablets) (ODB Formulary)

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B - Drug Regimen

fludarabine	25 mg /m²	PO	Days 1 to 5
(Outpatient prescription in multiples of 10 mg tablets)			
cyclophosphamide	150 mg /m²	PO	Days 1 to 5
(Round to nearest 10 mg)			
(Outpatient prescription in multiples of 25 or 50 mg tablets)			

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

For a usual total of 6 cycles unless disease progression or unacceptable toxicity occurs

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate – Consider prophylaxis daily

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Consider prophylactic growth factor support, antiviral and PCP prophylaxis (according to local practice).

If high volume disease (e.g. WBC > 25 x 10^9/L), consider prophylaxis for tumour lysis

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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

Toxicity	**Fludarabine (% previous dose)**	**Cyclophosphamide (% previous dose)**
Febrile Neutropenia; Grade 4 myelosuppression ≥ 7 days; Thrombocytopenic bleeding; 1-2 week delay prior cycle	75% or G-CSF (for isolated neutropenia*	75% or G-CSF (for isolated neutropenia)*
Grade 3 non-hematologic / organ	75%*	75%*
Any grade autoimmune, neurotoxicity, pneumonitis, pure red cell aplasia, > 2 week delay prior cycle, or progressive disease	Discontinue	Discontinue
*Do not retreat until non-hematologic / organ toxicity recovered to ≤ grade 2, ANC to ≥ 1 x 10^9/L and platelets ≥ 80 x 10^9/L (or to baseline levels)		

Hepatic Impairment

Bilirubin		**AST / ALT**	**Fludarabine (% usual dose)**	**Cyclophosphamide (% usual dose)**
1-2 x ULN			No data available; use with caution	No change
>2-4 X ULN	and/or	>2-4 X ULN		Caution
> 4 x ULN	and/or	> 4 x ULN		Caution

Renal Impairment

Creatinine Clearance (mL/min)	Fludarabine (% usual dose)	Cyclophosphamide (% usual dose)
>50 - 70	50%	100%
30 - 50	50%	75%
10 - <30	Discontinue	75%
<10		Use with extreme caution or Discontinue

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F - Adverse Effects

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

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Myelosuppression ± bleeding • Infection; including opportunistic (may be severe) • GI (nausea/vomiting, diarrhea, anorexia) • Fever • ↑ LFTs • Fatigue • Rash (may be severe) • Visual changes • Cystitis • Reproductive risks	• Autoimmune disorders (e.g. hemolytic anemia, TTP) • Encephalopathy, CNS toxicity (e.g. seizures, confusion, agitation) • Pneumonitis • Heart failure, arrhythmia • Arterial thromboembolism • Venous thromboembolism • SIADH • DIC • Secondary malignancies • VOD, HUS • Tumour lysis, renal failure • Pancreatitis • Rhabdomyolysis • Transfusion-associated graft-versus-host disease

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G - Interactions

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

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H - Drug Administration and Special Precautions

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

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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. Interim counts should be done in first cycle and repeated if dose modification necessary.
- Baseline and regular liver and renal function tests.
- Clinical toxicity assessment (including gastrointestinal, infection, autoimmune, dehydration, cystitis, pulmonary, skin, CNS effects); at each visit

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

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Cazin B, Divine M, Leprêtre S, et al. High efficacy with five days schedule of oral fludarabine phosphate and cyclophosphamide in patients with previously untreated chronic lymphocytic leukaemia. Br J Haematol. 2008 Oct;143(1):54-9.

Fludarabine, cyclophosphamide drug monographs, Cancer Care Ontario.

Laurenti L, De Padua L, Tarnani M, et al. Comparison between oral and intravenous fludarabine plus cyclophosphamide regime as front-line therapy in patients affected by chronic lymphocytic leukaemia: influence of biological parameters on the clinical outcome. Ann Hematol. 2011 Jan;90(1):59-65.

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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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