Regimen Monograph

A - Regimen Name

EPCO(RAMP) Regimen

Epcoritamab (Ramp-up)

EPCO Regimen

Epcoritamab

Disease Site

Hematologic
- Lymphoma - Non-Hodgkin's High Grade
- Lymphoma - Non-Hodgkin's Intermediate Grade

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 adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, DLBCL transformed from indolent lymphoma, high grade B-cell lymphoma (HGBCL), primary mediastinal B-cell lymphoma (PMBCL) or follicular lymphoma Grade 3B (FLG3b), after two or more lines of systemic treatment and who have previously received or are unable to receive CAR-T cell therapy

Supplementary Public Funding	**epcoritamab** New Drug Funding Program (Epcoritamab (Outpatient) - Relapsed or Refractory Diffuse Large B-Cell Lymphoma) **epcoritamab** High Cost Therapy Funding Program (Epcoritamab (Inpatient) - Relapsed or Refractory Diffuse Large B-Cell Lymphoma)

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B - Drug Regimen

Cycle 1:

epcoritamab	0.16 mg	Subcut	Day 1
epcoritamab	0.8 mg	Subcut	Day 8
epcoritamab	48 mg	Subcut	Days 15 and 22

Cycles 2 to 3:

epcoritamab	48 mg	Subcut	Days 1, 8, 15, 22

Cycles 4 to 9:

epcoritamab	48 mg	Subcut	Days 1 and 15

Cycles 10 and onwards:

epcoritamab	48 mg	Subcut	Day 1

Inpatient admission may be required for cytokine release syndrome (CRS) monitoring.

Note: ST-QBP funding for ambulatory administration only

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

Use regimen code EPCO(RAMP) for the first cycle, followed by EPCO for subsequent cycles.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

- Also refer to CCO Antiemetic Summary.

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

Pre-medications (prophylaxis for CRS):

Cycle 1:

Give 30 -120 minutes before each epcoritamab dose during Cycle 1:

- Dexamethasone 15 mg PO/IV (or equivalent)
- Diphenhydramine 50 mg PO/IV (or equivalent)
- Acetaminophen 650-1000 mg PO

Give after each epcoritamab dose during Cycle 1:

- Dexamethasone 15 mg PO/IV (or equivalent) x 3 days

Cycle 2 and onwards (only for patients who experienced Grade 2 or 3 CRS with previous dose):

Give 30 -120 minutes before each epcoritamab dose*:

- Dexamethasone 15 mg PO/IV (or equivalent)

Give after each epcoritamab dose*:

- Dexamethasone 15 mg PO/IV (or equivalent) x 3 days

*Continue to give with subsequent doses until Grade ≥ 2 CRS does not occur.

Other Supportive Care:

- Consider prophylaxis against Pneumocystis jirovecii pneumonia (PJP) and herpes virus infections.
- Consider other antimicrobial prophylaxis as per local guidelines.
- Epcoritamab should be administered to adequately hydrated patients.
- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

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E - Dose Modifications

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

Do not start treatment with epcoritamab in patients with active infection.

Dosage with toxicity

Table 1 - CRS and ICANS Toxicity Management

Recommendations below are based on the pivotal trial. Refer to Crombie et al. for alternative CRS and ICANS management guidelines.

Toxicity	Grade[a]	Management / Action	Next dose
CRS	Grade 1	Hold until CRS has resolved. Manage and treat symptoms as appropriate[b]: • Consider corticosteroid (e.g. dexamethasone). • Consider anticytokine therapy (e.g. tocilizumab) in certain cases.	Resume dose as recommended in Table 3.
	Grade 2	Hold until CRS has resolved. Manage and treat symptoms as appropriate[b]: • Tocilizumab IV as per institutional guidelines • Consider dexamethasone 10 - 20mg/ day (or equivalent). • If no improvement, initiate or increase dose of corticosteroid and consider alternative anticytokine therapy.	Administer pre-treatment medications prior to next dose. Monitor patient more frequently following next dose; consider hospitalization. Resume dose as recommended in Table 3.
	Grade 3	Hold until CRS has resolved. Manage and treat symptoms as appropriate[b]: • Tocilizumab IV as per institutional	Administer pre-treatment medications prior to next dose. Hospitalize for monitoring after next dose.

		guidelines • If no improvement, initiate or increase dose of corticosteroid and consider alternative anticytokine therapy. • Dexamethasone (e.g. 10 - 20mg IV q6h). If no response, initiate methylprednisolone IV 1000mg / day.	Resume dose as recommended in Table 3.
	Grade 4	Stop epcoritamab Manage and treat symptoms as appropriate[b]: • Tocilizumab IV as per institutional guidelines • If no improvement, initiate or increase dose of corticosteroid and consider alternative anticytokine therapy. • Dexamethasone (e.g. 10 - 20mg IV q6h). If no response, initiate methylprednisolone IV 1000mg / day.	Permanently discontinue.
ICANS	Grade 1	Hold until ICANS has resolved. Manage and treat symptoms as appropriate[b]: • Dexamethasone IV 10mg q12h • Consider seizure prophylaxis (e.g. levetiracetam).	Resume dose as recommended in Table 3.
	Grade 2	Hold until ICANS has resolved. Manage and treat symptoms as appropriate[b]: • Dexamethasone IV 10 - 20 mg q12h • Consider seizure prophylaxis (e.g. levetiracetam).	Resume dose as recommended in Table 3.
	Grade 3 (1st occurrence)	Hold until ICANS has resolved. Manage and treat symptoms as appropriate[b]:	Resume dose as recommended in Table 3.

		• Dexamethasone IV 10 - 20 mg q6h • If no response, initiate methylprednisolone IV 1000mg / day. • Consider seizure prophylaxis (e.g. levetiracetam).	
	Grade 3 (recurrent), or Grade 4	Stop epcoritamab. Manage and treat symptoms as appropriate[b]: • Dexamethasone IV 10 - 20 mg q6h • If no response, initiate methylprednisolone IV 1000mg / day. • Consider seizure prophylaxis (e.g. levetiracetam).	Permanently discontinue.

[a] Grade based on American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading (Lee et al 2019).

[b] Anticytokine therapy is recommended if ICANS occurs concurrently with CRS. Refer to EPCORE NHL-1 study protocol, or local institutional guidelines for management of concurrent CRS and ICANS.

Table 2 - Hematologic and Other Non-hematologic Toxicities

Toxicity	**Severity**	**Action**
Active Infection	Grade 1 to 3	Hold* until infection fully resolves.
	Grade 4	Hold* until infection fully resolves, OR Consider discontinue.
Neutropenia	ANC < 0.5 × 10^9/L	Hold* until ANC ≥ 0.5 × 10^9/L.
Thrombocytopenia	Platelets < 50 × 10^9/L	Hold* until platelets ≥ 50 × 10^9/L.
Other adverse effects	Grade ≥ 3	Hold* until toxicity improves to Grade ≤ 1. Consider discontinue for events associated with severe outcomes.

*Resume at dose described in Table 3

Table 3 - Recommended Restarting Doses After Dose Delay

Last Administered Dose	Time since Last Dose	Action for Next Dose
Step-up Dose 1 (0.16 mg)	> 8 days	Repeat Cycle 1 schedule starting at Step-up Dose 1 (0.16 mg), then resume the planned treatment schedule.
Step-up Dose 2 (0.8 mg)	≤ 14 days	Resume at 48 mg and resume planned treatment schedule.
	> 14 days	Repeat Cycle 1 schedule starting at Step-up Dose 1 (0.16 mg), then resume the planned treatment schedule.
Any Treatment Dose (48 mg)	≤ 42 days	Resume at 48 mg and resume planned treatment schedule.
	> 42 days	Repeat Cycle 1 schedule starting at Step-up Dose 1 (0.16 mg), then resume the planned treatment schedule.

Hepatic Impairment

Severity	Bilirubin		AST	Epcoritamab Dose
Mild	≤ ULN	AND	> ULN	No dose adjustment
	> 1 to 1.5 x ULN	AND	any	No dose adjustment
Moderate or Severe	> 1.5 x ULN	AND	any	No data

Renal Impairment

Severity	Creatinine Clearance (mL/min)	Epcoritamab Dose
Mild or Moderate	≥ 30	No dose adjustment
Severe or ESRD	< 30	No data

Dosage in the Elderly

No clinically meaningful differences in safety or efficacy were observed between patients ≥ 65 years of age compared with younger patients. Approximately one third of LBCL patients in the EPCORE NHL-1 trial were ≥ 65 years of age and 18% were ≥ 75 years of age.

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F - Adverse Effects

Refer to epcoritamab 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
• Cytokine release syndrome (may be severe)	• Fatigue • Injection site reaction • Myelosuppression ± infection (may be severe)	• Fever • Abdominal pain • Diarrhea • Nausea, vomiting • Rash, pruritus • Edema • Constipation • Headache • Anorexia • Arrhythmia • Musculoskeletal pain	• Immune effector cell-associated neurotoxicity syndrome (ICANS) • Pleural effusion • Hepatotoxicity • Hypogammaglobulinemia • Tumor lysis syndrome • Arterial or venous thromboembolism

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G - Interactions

Refer to epcoritamab drug monograph(s) for additional details.

- Epcoritamab may cause transient suppression of CYP450 enzymes. Monitor and adjust doses of CYP450 substrates with narrow therapeutic index (e.g. warfarin, cyclosporine) as necessary, especially after the first full dose (up to 72 hours after).

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H - Drug Administration and Special Precautions

Refer to epcoritamab drug monograph(s) for additional details.

Administration

- Epcoritamab should be administered by **subcutaneous injection only.**
- Certain doses of epcoritamab may require dilution; refer to product monograph for details on preparation.
- To minimize injection pain, allow solution to come to room temperature (for no more than 1 hour) before administration.
- Inject into lower abdomen (preferred) or thigh. Change injection site (from left to right or vice versa), especially during weekly administration (Cycles 1 - 3).
- Do not inject into areas where skin is red, bruised, scarred, tattooed or not intact.
- Monitor patients after administration of all doses in Cycle 1 and for 24 hours after the first full dose (Cycle 1, Day 15) for signs and symptoms of CRS or ICANS.
- Store unopened vials refrigerated (2°C to 8°C) and protect from light.

Contraindications

- Patients who are hypersensitive to this drug or to any of its components.

Warnings / Precautions

- Serious and life-threatening CRS and ICANS have occurred with epcoritamab, ensure step-up schedule is followed and infusions are administered where there is immediate access to

medications and equipment required to manage CRS and ICANS.
- Patients should avoid driving or operating heavy machinery if any new neurological symptoms present due to the risk of depressed level of consciousness from ICANS.
- Avoid administration of epcoritamab in patients with clinically significant active infections.
- Patients should not receive live or live-attenuated vaccines for at least 4 weeks prior to or during treatment with epcoritamab. The risk of vaccine-associated infection may be increased or immune response to vaccines may be reduced.
- Patients with high tumour burden or rapidly proliferative tumours, and patients with reduced renal function are at risk of tumour lysis syndrome.
- Patients with conditions such as LVEF < 45%, CNS involvement, allogenic HSCT or solid organ transplant, and impaired T-cell immunity were excluded from the clinical trial; assess benefit-risk of epcoritamab treatment in these patients.

Pregnancy / Lactation

- Epcoritamab is **not recommended** for use in pregnancy. IgG1 antibodies (such as epcoritamab) can cross placenta. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.

- Breastfeeding is **not recommended** during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).

- Fertility effects: Unknown

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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 dose; more frequently if clinically indicated
- Clinical toxicity assessment for CRS and ICANS; At each visit and for 24 hours after the first treatment dose (Cycle 1, Day 15)
- Renal function tests; Baseline and as clinically indicated
- Liver function tests; Baseline and as clinically indicated
- CRP, ferritin, coagulation tests (e.g. aPTT, INR, PT, fibrinogen); Baseline and as clinically indicated
- Electrolytes (e.g. K, Mg and PO4), uric acid levels; Baseline and as clinically indicated, especially for patients at risk of TLS
- Clinical toxicity assessment for infection, injection-site reactions, TLS, pulmonary and cardiac 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

Pharmacy Workload **(average time per visit)**
EPCO 17.00 minutes

Nursing Workload **(average time per visit)**
EPCO 44.833 minutes

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K - References

Crombie JL, Graff T, Falchi L, et al. Consensus recommendations on the management of toxicity associated with CD3×CD20 bispecific antibody therapy. *Blood* 2024; 143 (16): 1565–1575.

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

Lee W, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release Syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25:625-38.

Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a novel, subcutaneous CD3xCD20 Bispecific T-Cell-Engaging antibody, in relapsed or refractory large B-cell lymphoma: dose expansion in a phase I/II Trial. J Clin Oncol 2023 Apr 20;41(12):2238-47.

November 2024 Updated units in Dosage with Toxicity section.

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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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