Regimen Monograph

A - Regimen Name

BLIN Regimen

Blinatumomab

Disease Site

Hematologic
Leukemia - Acute Lymphoblastic (ALL)

Intent

Curative

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 patients with Philadelphia chromosome negative (Ph-), CD19 positive (CD19+), B-cell precursor acute lymphoblastic leukemia (BCP-ALL) who are in first or second hematologic complete remission (CR) and are minimal residual disease positive (MRD+)*

- Patients should have received, over the course of their treatment for BCP-ALL, a minimum of 3 intensive chemotherapy blocks of a treatment regimen that is age-appropriate and given with curative intent before proceeding to blinatumomab therapy.

*defined as MRD detected at a level ≥ 0.1% (i.e., $\geq 10^{-3}$)

Supplementary Public Funding	**blinatumomab** New Drug Funding Program (Blinatumomab - Minimal Residual Disease (MRD)-Positive B-cell Precursor Acute Lymphoblastic Leukemia)
Additional Information	The information provided in this document is intended for use in the management of adults with leukemia only and for cancer centres with expertise in treating acute leukemia.

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B - Drug Regimen

Patients ≥45 kg (fixed dose):

blinatumomab	28 mcg /day	IV continuous infusion Days 1 to 28*

OR

Patients <45 kg (BSA-based dosing):

blinatumomab	15 mcg /m²/day	IV continuous infusion Days 1 to 28*

* Each cycle is separated by a 2-week treatment-free interval.

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C - Cycle Frequency

REPEAT EVERY 42 DAYS

Continue until unacceptable toxicity, hematologic relapse, MRD relapse, treatment with hematopoietic stem cell transplant (HSCT), or up to the completion of 4 cycles.

(Maintenance or consolidation therapy after HSCT is not funded)

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

- Also refer to CCO Antiemetic Recommendations.

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 infusion reaction):
(in adults ≥ 18 years of age)

- Dexamethasone 16 mg or equivalent (e.g. Prednisone 100 mg IV) 1 hour before the first dose of each cycle.
- An antipyretic is recommended during the first 48 hours of each cycle.

Other Supportive Care:

- CNS prophylaxis with intrathecal chemotherapy (before and during treatment) is recommended.
- Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.
- Consider prophylaxis against Pneumocystis jirovecii pneumonia (PJP) and herpes virus infections.
- Consider other antimicrobial prophylaxis as per local guidelines.
- Hospitalization is recommended for, at minimum, the first 3 days of cycle 1 and the first 2 days of cycle 2, to monitor for infusion reactions that are clinically indistinguishable from cytokine release syndrome (CRS).

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E - Dose Modifications

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

Dosage with toxicity

Dose should be withheld or discontinued for toxicity as recommended.

Toxicity	Grade	Patients ≥ 45kg	Patients < 45kg
Neurotoxicity (including ICANS)	Grade 3	Hold until recovery to ≤ Grade 1 for at least 3 days. Restart at 9 mcg/day. Increase to 28 mcg/day after 7 days if toxicity does not recur. Pre-medicate with up to 24 mg dexamethasone with a 4-day taper. Consider a non-sedating anticonvulsant medication. Discontinue if toxicity occurred at 9 mcg/day, or if toxicity takes more than 7 days to resolve.	Hold until recovery to ≤ Grade 1 for at least 3 days. Restart at 5 mcg/m^2/day. Increase to 15 mcg/m^2/day after 7 days if toxicity does not recur. Pre-medicate with dexamethasone (e.g. up to 20 mg) and taper the dose. Consider a non-sedating anticonvulsant medication. Discontinue if toxicity occurred at 5 mcg/m^2/day, or if toxicity takes more than 7 days to resolve.
	Grade 4	Discontinue.	
	Seizure	If >1 seizure, discontinue.	
Cytokine Release Syndrome	Grade 3	Hold until recovery to ≤ Grade 1. Restart at 9 mcg/day. Increase to 28 mcg/day after 7 days if toxicity does not recur.	Hold until recovery to ≤ Grade 1. Restart at 5 mcg/m^2/day. Increase to 15 mcg/m^2/day after 7 days if toxicity does not recur.
	Grade 4	Discontinue.	Discontinue.

LFTs > 5 x ULN or Bilirubin > 3 x ULN		Hold until recovery to ≤ Grade 1. Consider restarting at 9 mcg/day. If appropriate, increase to 28 mcg/day after 7 days if toxicity does not recur. Discontinue if toxicity does not resolve within 14 days.	Hold until recovery to ≤ Grade 1. Consider restarting at 5 mcg/m^2/day. If appropriate, increase dose to 15 mcg/m^2/day after 7 days if toxicity does not recur. Discontinue if toxicity does not resolve within 14 days.
Other clinically relevant toxicity	Grade 3	Hold until recovery to ≤ Grade 1. Restart at 9 mcg/day. Increase to 28 mcg/day after 7 days if toxicity does not recur. Discontinue if toxicity does not resolve within 14 days.	Hold until recovery to ≤ Grade 1. Restart at 5 mcg/m^2/day. Increase dose to 15 mcg/m^2/day after 7 days if toxicity does not recur. Discontinue if toxicity does not resolve within 14 days.
	Grade 4	Consider discontinuing.†	
Suspected Pancreatitis		Hold and investigate. Consider discontinuing if confirmed.	
Suspected leukoencephalopathy		Hold and consider neurologist consultation, brain MRI and examination of CSF. Discontinue if confirmed.	
Capillary leak syndrome, Disseminated intravascular coagulation		Hold until recovery. Weigh benefit vs. risk to discontinue or restart.	

* If dose held for less than 1 week, resume same cycle. If dose held for more than 1 week, start a new cycle.

† Discontinue for grade 4 cytokine release syndrome.

Management of Infusion-related reactions (including Cytokine Release Syndrome (CRS)):

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • After resolution of all symptoms, treatment can be resumed. • Consider administering dexamethasone when restarting an infusion after an interruption of ≥ 4 hours.	See restart.
3	• Stop treatment. • Aggressively manage symptoms. **Restart:** • After resolution of all symptoms, treatment can be resumed. • Consider administering dexamethasone when restarting an infusion after an interruption of ≥ 4 hours. If patient is ≥ 45 kg: • Resume at 9 mcg/day, with an escalation to 28 mcg/day after 7 days if the infusion reaction does not recur If patient is < 45 kg: • Resume at 5 mcg/m^2/day, with an escalation to 15 mcg/m^2/day after 7 days if the infusion reaction does not recur	See restart.
4	• Stop treatment. • Aggressively manage symptoms.	Permanently discontinue (do not re-challenge).

Hepatic Impairment

No formal pharmacokinetic studies have been conducted in patients with hepatic impairment. Hepatic impairment does not appear to have an effect on blinatumomab clearance.

Renal Impairment

No formal pharmacokinetic studies have been conducted in patients with renal impairment. No information is available in severe renal impairment (CrCl < 30 ml/min) or in patients on hemodialysis.

Dosage in the Elderly

Age does not appear to change the pharmacokinetics of blinatumomab. Patients over age 65 experienced a higher rate of serious neurological events compared to younger patients, including encephalopathy, confusion and cognitive disorders. Serious infections were also more common in older patients.

Children:

Refer to the product monograph for comprehensive pre-medication and dosing information in this population.

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F - Adverse Effects

Refer to blinatumomab 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
• Fever	• Infusion related reaction (may be severe) • Headache • Myelosuppression ± infection, bleeding (may be severe)	• Edema • ↑ LFTs • Cough, dyspnea • Rash • Cytokine release syndrome • Musculoskeletal pain • Hypotension • Insomnia • Tremor • Decreased immunoglobulins	• Peripheral neuropathy • Cranial neuropathy • ICANS • Tumour lysis syndrome • Hypersensitivity • Hemophagocytic histiocytosis • Pancreatitis

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G - Interactions

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

- Blinatumomab may suppress CYP450 via transient release of cytokines. Monitor and adjust the dose of narrow therapeutic range CYP 2C9 and 3A4 substrates (e.g. warfarin and cyclosporine). This is especially important during the first 9 days of the first cycle and the first 2 days of the 2nd cycle.

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H - Drug Administration and Special Precautions

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

Administration

Refer to the Product Monograph for detailed preparation and administration information.

- Medication errors have been reported with blinatumomab. Instructions for preparation and administration should be strictly followed.
- In patients < 45 kg, blinatumomab must be dosed based on body surface area calculations (mcg/m^2/day) and not at the fixed mcg/day dosing regimen.
- 7-day bags of blinatumomab solution for infusion, which contain benzyl alcohol as a preservative, are not recommended for use in neonates, infants, or patients weighing < 22 kg, due to potential serious and fatal adverse reactions (eg. gasping syndrome).
- Blinatumomab is compatible with polyolefin, PVC (non-DEHP), or EVA infusion bags/pump cassettes and tubing sets. It is incompatible with DEHP equipment due to possible particle formation.
- The IV tubing should contain an in-line, sterile, non-pyrogenic, low protein-binding 0.2 or 0.22 micron filter (for 24h, 48h, 72h, or 96h infusions).
- An in-line filter is **NOT** required for a 7-day bag (based on preparation procedure in product monograph).
- Prime the IV tubing **only** with the solution in the bag containing the final prepared blinatumomab solution for infusion.
- Blinatumomab is administered by continuous IV infusion using an infusion pump. The pump should be programmable, lockable, non-elastomeric and have an alarm.
- Infuse through a dedicated lumen; **DO NOT** flush infusion lines into the patient. Inadvertent excess dosage may be given as the infusion bag contains overfill to account for tubing priming volume.

Infusion rates for fixed dose:

Infusion rate (mL/h)	Duration of infusion (hour)	Total dose volume (mL)	Overfill in bag (mL)*
10	24	240	~35-45 mL, depending on the dose and the infusion duration
5	48	240	
3.3	72	237.6	
2.5	96	240	
0.6	168 (7 days)	100.8	~10 mL

*based on preparation instructions in product monograph

Storage / Stability:

- Refrigerate unopened vials (including IV solution stabilizer) in original package between 2-8^{o}C.
- Protect from light. Do not freeze.
- Refer to the product monograph for storage requirements of reconstituted or diluted solutions. Storage times include infusion time. If IV bag of solution for infusion is not administered within the time frames and temperatures indicated, discard; do not refrigerate again.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications:

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

Warnings / Precautions:

- Patients with high leukocyte counts and/or high tumour burden as well as those with moderate renal impairment are at risk of tumour lysis syndrome. Prophylaxis and close monitoring should be considered.
- Vaccination with live viral vaccines is not recommended for at least 2 weeks prior to the start of treatment, during treatment, and until recovery of the B lymphocytes to normal range following the last cycle. If blinatumomab exposure occurred during pregnancy, the infant's B lymphocytes should be monitored and deemed within the normal range prior to administration of live vaccines.
- There is limited experience with blinatumomab in patients with a history of neurological events or with active ALL in the CNS.
- There is limited experience with blinatumomab in patients with active uncontrolled infections.
- Patients who have received prior cranial irradiation and chemotherapy (i.e. high dose methotrexate or intrathecal cytarabine) are at increased risk of encephalopathy and should be monitored closely.
- Blinatumomab is not recommended for patients with CD-19 negative disease.
- Lineage switch from ALL to AML has been reported in patients receiving blinatumomab. Close monitoring is recommended in patients with documented immunophenotypic and/or cytogenetic abnormalities at initial diagnosis of B-precursor ALL.
- Due to the potential for neurological events, including seizures, patients should refrain from driving and engaging in hazardous tasks or activities while receiving blinatumomab.

Pregnancy / Lactation:

- This regimen is not recommended for use in pregnancy. 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: Unlikely

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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, before each cycle, and as clinically indicated
- Liver function tests; Baseline and before each cycle
- Neurological exam; Baseline and as clinically indicated
- Signs and symptoms of TLS, including renal function and fluid balance; In the first 48 hours of the first infusion; thereafter as clinically indicated
- Clinical toxicity assessment for infusion reactions (including cytokine release syndrome), infections, bleeding, GI effects, pancreatitis, edema, neurological events; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	0.5 hour (connection to IV pump)
Pharmacy Workload (average time per visit)	35.99 minutes
Nursing Workload (average time per visit)	76.29 minutes

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K - References

Blinatumomab drug monograph, Ontario Health (Cancer Care Ontario).

Gökbuget N, Zugmaier G, Dombret H, et al. Curative outcomes following blinatumomab in adults with minimal residual disease B-cell precursor acute lymphoblastic leukemia. Leuk Lymphoma 2020 Nov;61(11):2665-73.

Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 2018;131(14):1522-31.

October 2024 Modified Premedication and Supportive Measures, Dose Modifications, Adverse Effects, Drug Administration and Special Warnings/Precautions 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.

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.

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