Canadian Association of Nurses in Oncology
Association canadienne des infirmières en oncologie

This program meets Canadian Association of Nurses in Oncology (CANO/ACIO) guidelines and is expected to support nurses in their understanding of blinatumomab continuous infusion for B-Cell Precursor Acute Lymphoblastic Leukemia. Endorsement is provided by CANO/ACIO for a time period of two years, ending January 2, 2025.

Clinical Practice Resource: A Practical Guide to Blinatumomab Continuous Infusion for Adult Patients with B-Cell Precursor Acute Lymphoblastic Leukemia

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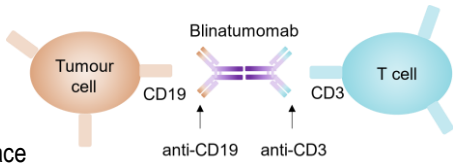
RESOURCE FACULTY: Danielle Brandys, NP (Princess Margaret Cancer Center, ON), Kari Kolm, NP (Hamilton Health Sciences, ON), Phillippe Bouchard, BPharm, MSc, BCOP (Hôpital Maisonneuve-Rosemont, QC)

IMPORTANT:

- Safe delivery of blinatumomab therapy requires attention to preparation, administration, monitoring, and coordination of care.
- The guidance provided in this resource mainly pertains to patients weighing ≥ 45 kg. Please refer to the BLINCYTO Product Monograph for dosing, administration, and toxicity management for patients weighing < 45 kg and pediatric patients.
- This clinical resource is intended to provide practical guidance where local resources may not exist; institutional guidelines around dose reductions, toxicity management, and infusion line and intravenous catheter care should be followed. However, precautions must be taken to AVOID FLUSHING INFUSION LINE OR INTRAVENOUS CATHETER CONTAINING BLINATUMOMAB SOLUTION.
- Single-centre examples of infusion line and intravenous catheter care are provided for consideration where generalized nursing guidance has not been published. Consult with local nursing staff leads for protocols regarding IV catheter care in patients receiving blinatumomab.

1. Introduction: Blinatumomab in B-Cell Precursor Acute Lymphoblastic Leukemia

BITE TECHNOLOGY AND BLINATUMOMAB MECHANISM OF ACTION



- Blinatumomab is a type of immunotherapeutic agent called a bispecific T-cell engager (BiTE).[1]
- BiTE therapies are bispecific antibodies designed to recognize two different cell surface antigens to facilitate binding of T-cells to tumour cells, leading to tumour cell lysis.[1]
- Blinatumomab recognizes antigens CD19 (expressed on B-cells including tumour cells) and CD3 (expressed on cytotoxic T-cells).[1]
- Binding of CD19+ cells to CD3+ cells causes T-cell-induced lysis of both benign and malignant B-cells.[1]
- Approximately 75% of acute lymphoblastic leukemia (ALL) is of B-cell lineage and 25% is of T-cell lineage; therefore, blinatumomab can be used in the majority of ALL.[2]

BLINATUMOMAB IN ADULT B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA (BCP-ALL)

- Conventional treatment of BCP-ALL with multiple chemotherapeutic agents leads to initial complete remission (CR) in most adult patients. However, long-term efficacy is limited due to poor chemotherapy tolerance, advanced age, and higher rate of relapse as 30-60% of patients with ALL relapse with multi-drug conventional chemotherapy regimens.[3,4]
- In addition, prior to B-cell targeted treatments, previous salvage chemotherapies had very low rates of remission.[5]
- Allogeneic hematopoietic stem cell transplantation (HSCT) is recommended as a curative approach for many high-risk patients with relapsed or refractory ALL.[3,4] However, detectable minimal residual disease (MRD+) pre-HSCT is associated with a higher rate of relapse following HSCT.[6]
- Blinatumomab may increase the potential for more patients to benefit from HSCT; as a single agent, blinatumomab has demonstrated the ability to achieve:[1,3]
  - complete remission in patients with relapsed/refractory BCP-ALL[1,3]
  - MRD negativity in patients with Philadelphia chromosome-negative BCP-ALL in hematological CR1 or CR2 with persistent MRD (MRD+)[1,3]
- By more specifically targeting tumour cells, blinatumomab has also exhibited fewer overall adverse events compared to conventional chemotherapy regimens for relapsed/refractory BCP-ALL.[3]

1.1: Key Trials Of Blinatumomab In Patients With B-Cell Precursor Acute Lymphoblastic Leukemia[7]

Trial	Population	Intervention	Primary Endpoint Outcome	
MRD+ ALL				
BLAST (NCT01207388) STUDY MT102-203 Phase 2, confirmatory multicentre, open-label, single-arm study (N=116)	• Adult patients in CR with persistent MRD (≥10^{-3}) of BCP-ALL • Included Philadelphia chromosome-positive and negative BCP-ALL	• Blinatumomab CIV x 4 weeks followed by 2 weeks off [Median # cycles = 2; range 1-4]	**% Complete MRD Response Within 1 Treatment Cycle**	88/113 (77.9%)
Relapsed/Refractory ALL				
TOWER (NCT02013167) STUDY 00103311 Phase 3, randomized, open-label study (N=405)	• Adult subjects with Philadelphia chromosome-negative relapsed/refractory BCP-ALL	• Blinatumomab vs SOC* chemotherapy • Blinatumomab CIV x 4 weeks followed by 2 weeks off [Median # cycles = 1; range 0-9]	**Overall Survival, Median (mo) HR**	**BLIN** / **SOC*** 7.7 / 4.0 HR = 0.71 P = 0.012
ALCANTARA (NCT02000427) STUDY 20120216 Phase 2, open-label, single-arm, multicentre study (N=45)	• Adult subjects with relapsed/refractory Philadelphia chromosome-positive BCP-ALL	• Blinatumomab CIV x 4 weeks followed by 2 weeks off [Median # cycles = 2; range 1-5]	**CR/CRh During First 2 Cycles**	16/45 (35.6%)

*SOC, standard of care (1 of 4 prespecified, investigator-selected chemotherapy regimens). BLIN, blinatumomab; CIV, continuous IV infusion; CR, complete remission; CRh, complete remission with partial hematologic recovery; HR, hazard ratio.

2. Blinatumomab Indications for Use in Adult BCP-ALL

2.1: Health Canada Indications For Blinatumomab In Adult B-Cell Precursor Acute Lymphoblastic Leukemia[7]

MRD+ BCP-ALL	• Patients with Philadelphia chromosome-negative CD19-positive B-cell precursor acute lymphoblastic leukemia in first or second hematologic complete remission with minimal residual disease (MRD) ≥ 0.1%* • This indication is a market authorization with conditions (NOC/c), pending clinical trial results to verify its clinical benefit.
Relapsed or Refractory BCP-ALL	• Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia

*Guidance for the treatment of pediatric patients is beyond the scope of this resource. NOC/c, Notice of Compliance with conditions.

3. Blinatumomab Dosing

MRD+ BCP-ALL DOSING GUIDANCE

- Blinatumomab is administered as a continuous intravenous infusion (CIV), delivered at a constant flow rate using an infusion pump.[7]
- A single cycle is 28 days of continuous infusion followed by a 14-day treatment-free interval.[7]
- Course of therapy: patients may receive 1 cycle of blinatumomab as induction treatment followed by 3 cycles of blinatumomab as consolidation treatment.[7]

3.1: Course of Therapy for MRD+ BCP-ALL[7]

Cycle 1		Cycle 2		Cycle 3		Cycle 4	
Induction		Consolidation		Consolidation		Consolidation	
Day 1-28	Day 29-42	Day 1-28	Day 29-42	Day 1-28	Day 29-42	Day 1-28	Day 29-42
Blinatumomab	—	Blinatumomab	—	Blinatumomab	—	Blinatumomab	—

3.2: Blinatumomab Dosing and Co-Medication Guidance for MRD+ BCP-ALL[7]

	Cycle 1: Induction (42 days)	Cycles 2: Consolidation (42 days)	Cycles 3-4: Consolidation (42 days)
CNS Prophylaxis	• Intrathecal chemotherapy prophylaxis recommended before and during blinatumomab	• Intrathecal chemotherapy prophylaxis recommended before and during blinatumomab	• Intrathecal chemotherapy prophylaxis recommended before and during blinatumomab
Treatment Setting	• Hospitalization is recommended, at minimum for days 1 to 3	• Hospitalization is recommended, at minimum for days 1 and 2	• Healthcare professional (HCP) supervision or hospitalization is recommended for cycle starts
Premedication	• Premedication: Prednisone 100 mg equivalent (e.g., dexamethasone 16 mg) IV 1 hour prior to blinatumomab on day 1	• Premedication: Prednisone 100 mg equivalent (e.g., dexamethasone 16 mg) IV 1 hour prior to blinatumomab on day 1	• Premedication: Prednisone 100 mg equivalent (e.g., dexamethasone 16 mg) IV 1 hour prior to blinatumomab on day 1
Blinatumomab Dose: Patient Weight ≥ 45 kg (fixed dose)	• Day 1-28: 28 mcg/day CIV	• Day 1-28: 28 mcg/day CIV	• Day 1-28: 28 mcg/day CIV
Treatment-free Interval	• Day 29-42 (14 days)	• Day 29-42 (14 days)	• Day 29-42 (14 days)
Treatment Interruption Guidance	• If treatment interrupted for ≥ 4 hours: – Healthcare professional supervision or hospitalization is recommended for re-initiation[7] • If treatment interruption is ≤ 7 days, continue same cycle to a total of 28 days of infusion (including days before and after missed dose in that cycle).[7] • If treatment interruption is > 7 days, start a new cycle.[7]		

Refer to the BLINCYTO Product Monograph for patients weighing < 45 kg. The efficacy of blinatumomab for the treatment of MRD+ BCP-ALL in patients weighing < 45 kg has not been established in clinical trials.[7] CNS, central nervous system.

RELAPSED OR REFRACTORY BCP-ALL DOSING GUIDANCE

- Blinatumomab is administered as a continuous intravenous infusion (CIV), delivered at a constant flow rate using an infusion pump.[7]
- A single cycle is 28 days of continuous infusion followed by a 14-day treatment-free interval for induction and consolidation phases; for maintenance cycles, the treatment-free interval is 56 days.[7]
- Course of therapy: patients may receive 2 cycles of blinatumomab as induction treatment followed by 3 cycles of blinatumomab as consolidation treatment, and up to 4 cycles of blinatumomab as maintenance therapy.[7]

3.3: Course of Therapy for Relapsed or Refractory BCP-ALL[7]

Cycle 1 and 2		Cycle 3, 4 and 5		Up to 4 Cycles (Cycle 6, 7, 8, and 9)	
Induction		Consolidation		Maintenance	
Day 1-28	Day 29-42	Day 1-28	Day 29-42	Day 1-28	Day 29-84
Blinatumomab	—	Blinatumomab	—	Blinatumomab	—

3.4: Blinatumomab Dosing and Co-Medication Guidance for Relapsed or Refractory BCP-ALL[7]

	Cycle 1	Cycle 2	Cycle 3, 4 and 5	Up to 4 Cycles (Cycle 6, 7, 8, and 9)
	Induction	Induction	Consolidation	Maintenance
CNS Prophylaxis	• Intrathecal chemotherapy prophylaxis recommended before and during blinatumomab	• Intrathecal chemotherapy prophylaxis recommended before and during blinatumomab	• Intrathecal chemotherapy prophylaxis recommended before and during blinatumomab	• Intrathecal chemotherapy prophylaxis recommended before and during blinatumomab
If High Tumour Burden (≥ 50% leukemic blasts in bone marrow or > 15 x 10^9/L peripheral blood leukemic blast count)	• Dexamethasone (not to exceed 24 mg/day) for up to 4 days prior to first dose of blinatumomab			
Treatment Setting	• Hospitalization recommended at a minimum for days 1 to 9 of Cycle 1	• Hospitalization recommended for days 1 to 2 of Cycle 2	• HCP supervision or hospitalization is recommended for cycle starts	• HCP supervision or hospitalization is recommended for cycle starts
Premedication	• Premedication: Dexamethasone 20 mg IV 1 hour prior to blinatumomab on day 1 • Consider premedication with dexamethasone prior to dose escalation*[1,4,8]	• Premedication: Dexamethasone 20 mg IV 1 hour prior to blinatumomab on day 1	• Premedication: Dexamethasone 20 mg IV 1 hour prior to blinatumomab on day 1	• Premedication: Dexamethasone 20 mg IV 1 hour prior to blinatumomab on day 1
Blinatumomab Dose: Patient Weight ≥ 45 kg (fixed dose)	• Day 1-7: 9 mcg/day • Day 8-28: 28 mcg/day	• Day 1-28: 28 mcg/day	• Day 1-28: 28 mcg/day	• Day 1-28: 28 mcg/day
Treatment-free Interval	• Day 29-42 (14 days)	• Day 29-42 (14 days)	• Day 29-42 (14 days)	• Day 29-84 (56 days)
Treatment Interruption Guidance	• If treatment interrupted for ≥ 4 hours: – Healthcare professional supervision or hospitalization is recommended for re-initiation[7] – Consider premedication with dexamethasone (20 mg IV) prior to re-initiation*[1,4,8] • If treatment interruption is ≤ 7 days, continue same cycle to a total of 28 days of infusion (including days before and after missed dose in that cycle).[7] • If treatment interruption is > 7 days, start a new cycle.[7]			

Refer to the BLINCYTO Product Monograph for patients weighing < 45 kg.

*Recommended in US Prescribing Information,[8] not Health Canada-approved.

4. Administration

- Blinatumomab medication errors (including underdose and overdose) have occurred. Strictly follow preparation and administration instructions.[7]

BLINATUMOMAB TREATMENT OVERVIEW

- Blinatumomab is delivered as a 28-day continuous IV infusion.[7]
- Blinatumomab IV bags may be prepared for delivery over 24 hours, 48 hours, 72 hours, 96 hours, or 7 days, to make up the 28-day continuous infusion.[7]
- Hospitalization is required initially for the first two cycles to monitor and manage toxicities such as infusion reactions, Cytokine Release Syndrome (CRS), Tumour Lysis Syndrome (TLS), and neurological toxicity; once tolerability is established, clinically stable patients may be transitioned to the outpatient setting with frequent follow up with their healthcare team.[4,9]
  - Consolidation and maintenance cycles (cycle ≥ 3) can also be given safely in the outpatient setting with close monitoring and proper support at home.
- Due to the higher risk for serious toxicities during the initial hours and days of infusion, treatment cycles should be initiated in the hospital during daytime hours.[7,9]
- The timing of blinatumomab infusion initiation on day 1 of a cycle should consider:[9]
  - When there are sufficient resources to monitor and address any toxicities or questions
  - The timing for outpatient administration (if and when appropriate), given the requirement for precise timing of IV bag changes
- Minimum weekly clinic visits are advised in the outpatient setting, ensuring a knowledgeable healthcare team member is available at all times[4,10]; some centres perform twice-weekly bag changes with patient assessment and weekly blood work.

INFUSION DURATION AND RATE

- Blinatumomab IV bags may be prepared for continuous infusion over 24 hours, 48 hours, 72 hours, 96 hours, or 7 days.[7]
  - For infusion durations ≤ 96 hours, a preservative-free blinatumomab solution is used.[7]
  - For infusion durations of 7 days, the blinatumomab solution is prepared with bacteriostatic saline (containing benzyl alcohol).[7]
- The infusion rate depends on the prescribed infusion duration. The treating physician should choose the infusion duration, considering weight of patient and the timing/frequency of infusion bag changes.[7]

4.1: Infusion Rates by Duration and Dose for Patients Weighing ≥ 45 kg*

Infusion Duration	Dose	Infusion Rate	Blinatumomab Concentration†
24 Hours	9 mcg/day	10 mL/hour	0.038 mcg/mL
	28 mcg/day	10 mL/hour	0.12 mcg/mL
48 Hours	9 mcg/day	5 mL/hour	0.077 mcg/mL
	28 mcg/day	5 mL/hour	0.23 mcg/mL
72 hours	9 mcg/day	3.3 mL/hour	0.11 mcg/mL
	28 mcg/day	3.3 mL/hour	0.35 mcg/mL
96 Hours	9 mcg/day	2.5 mL/hour	0.15 mcg/mL
	28 mcg/day	2.5 mL/hour	0.467 mcg/mL
7 Days	28 mcg/day	0.6 mL/hour	1.91 mcg/mL

*See BLINCYTO Product Monograph for infusion rates for patients < 45 kg.

†The total volume of solution is calculated from the volume of reconstituted blinatumomab solution, IV solution stabilizer, and normal saline required for each infusion duration and dose. Note, the IV tubing is primed with the final blinatumomab solution in the IV bag.

EQUIPMENT AND COMPATIBILITY

- Blinatumomab is **incompatible** with di-ethylhexyl phthalate (DEHP).[7]
- Do **not** use an in-line filter for a 7-day infusion.[7]

4.2: Equipment and Storage Requirements

Equipment	Recommendations		
Ports and IV catheters	• Infuse blinatumomab through a dedicated lumen (e.g., peripherally inserted central catheter [PICC] or Hickman line) to ensure continuous (non-interrupted) infusion of blinatumomab and access for additional IV medications and laboratory draws.[4] – Some practices do not use PICCs due to concerns about infection risk and thrombosis.[9] • For patients with an implanted port, peripherally draw laboratory samples to avoid interrupting blinatumomab treatment.[4]		
Infusion Bags and Tubing	• Infusion bags – Polyolefin, PVC **non**-di-ethylhexyl phthalate (DEHP-free), or ethyl vinyl acetate (EVA) infusion bags.[7] • Infusion tubing – Polyolefin, PVC DEHP-free, or EVA intravenous tubing sets.[7] – Ensure IV tubing is compatible with infusion pump.[7]		
Filter	• For 24-hr, 48-hr, 72-hr, and 96-hr infusions:[7] – Use a sterile, non-pyrogenic, low protein-binding 0.2 or 0.22 micron in-line filter. • For 7-day infusions:[7] – **Do not** use an in-line filter.		
Infusion Pump	• Use an approved infusion pump[10] • The infusion pump should:[7] – Be programmable, lockable, non-elastomeric.[7] – Have an alarm[7] (visual and auditory).[10] • Ensure infusion pump is compatible with IV tubing.[7]		
Storage and Stability	• Store IV tubing and bag at 2°C to 8°C if not used immediately.[7] • Do not freeze.[7] • Prepared blinatumomab infusion bags do not need to be protected from ambient lighting. – Some centres may choose to dispense blinatumomab in brown UV light protectant bags.		
	Maximum Storage (+ Infusion) Time* of Prepared Blinatumomab Infusion Bag:[7]		
	Temperature	**Preservative-free (≤ 96-hr infusion)**	**With preservative (7-day infusion)**
	Room temperature (23°C to 27°C)	96 hours	7 days
	Refrigeration (2°C to 8°C)	10 days	14 days

*Maximum storage time including infusion time. If infusion bag containing final prepared blinatumomab solution is not administered within indicated timeframes and temperatures, discard (do not refrigerate again).[7] PVC, polyvinyl chloride.

ADMINISTRATION GUIDANCE

4.3: Blinatumomab Administration Guidance

Administering Blinatumomab	
Patient Assessment and Premedication	• See Baseline Assessment (section 6) and Suggested Monitoring (section 8). • Ideally patient should have a double-lumen[4] (e.g., peripherally inserted central catheter (PICC) or Hickman line). – One lumen dedicated for blinatumomab and the second lumen for laboratory draws and other IV medications.[4] • If patient has an implanted port, draw laboratory sample peripherally to avoid interruption in therapy.[4] • Premedicate with dexamethasone (see Dosing 3.2, 3.4). • Other prophylactic measures, as appropriate: – Hydration – Antihyperuricemic therapies (allopurinol or rasburicase)[7] – Antipyretics (recommended during the first 48 hours of each cycle)[11]
Inspection of Infusion Bag and Tubing	• IV tubing and filter will have been attached and the tubing primed with the final blinatumomab solution during pharmacy preparation.[7] – An in-line filter should NOT be used for a 7-day infusion.[7]

…continued

	• Ensure the blinatumomab bag and tubing has been stored properly prior to administration (see section 4.2). • Visually inspect reconstituted blinatumomab solution for particulate matter and discoloration.[7] • Solution should be clear to slightly opalescent, colourless to slightly yellow.[7] • DO NOT use if solution is cloudy or has precipitated.[7] • Blinatumomab bags will always have overfill to ensure patient receives the full blinatumomab dose.[7] – For 24-hr, 48-hr, 72-hr, and 96-hr infusions: the starting volume is 270 mL (240 mL administered to patient).[7] – For 7-day infusions: the final volume of infusion solution is 110 mL (100 mL administered to patient).[7]
Preparation for Infusion	• IMPORTANT: Do not flush blinatumomab infusion line or IV catheter containing blinatumomab solution. • Day 1 only, before initiating blinatumomab: Ensure catheter being used has a brisk blood return (can aspirate ≥ 3 mL in ≤ 3 seconds) and flushes easily.[4] – If necessary, obtain an order for clearing agent before initiating therapy and flush catheter well with 20 mL of 0.9% sodium chloride.[4] • Infuse blinatumomab through a dedicated lumen[7] (e.g., PICC or Hickman line). • Follow instructions on pharmacy label of prepared bag; infuse prepared blinatumomab infusion solution at the specified constant infusion rate.[7] • The slow infusion rate and in-line filter increase risk of blood back-up into the IV administration set.[4] • To prevent blood from backing up into IV administration equipment, some practices recommend positioning the patient and equipment as follows (particularly for slow infusion rates):[4] – Ensure filter does not hang below patient's catheter. – Ideally the infusion pump should be below or at the level of patient's heart.
Infusion Bag Changes	• IMPORTANT: Do not flush blinatumomab infusion line or IV catheter containing blinatumomab solution, especially during infusion bag change.[7] Ensure no blinatumomab solution is present in the IV catheter before flushing. – Flushing blinatumomab solution (when changing bags or at infusion completion) can cause excess dosage from accidental bolus administration and complications including cytokine release syndrome (CRS).[4,7] – As an example, Cancer Care Manitoba recommends if accessing the lumen, first withdraw 2 mL of blood (containing drug), then flush.[12] • Change infusion bag at the same time each day, according to the chosen infusion duration, independent of the remaining volume.[4] – Re-check infusion rate at each bag change; a change in bag format requires a change of the infusion rate. • When administering with a multi-lumen venous catheter, infuse blinatumomab through a dedicated lumen.[7] • Discard unused blinatumomab solution in the IV bag and the tubing according to local requirements.[7] **Maintaining Catheter Patency (Data on file, Amgen, 2016)** • Follow institutional policy, provided there is no flushing of blinatumomab. • Steps include: – Disconnect blinatumomab IV bag – Withdraw blood through line to clear line of blinatumomab (blood volume not specified) – Flush with saline per institutional practice **Catheter Occlusion (guidance from University of Maryland Medical Centre)[4]** • DO NOT FLUSH; flushing of occluded catheter could cause an adverse event. • A fully occluded catheter requires removal and replacement; notify physician with goal of keeping treatment interruption to < 4 hours.[4] • Attempt to aspirate occluded catheter.[4] – If blood return is successful, remove 5 mL blood (to remove residual drug), then flush with 0.9% sodium chloride. Restore patency using clearing agent. – If the patient has a PICC, move infusion to other lumen. – For implanted port, initiate peripheral catheter to ensure continuous administration. – If aspiration from catheter fails, DO NOT FLUSH. Contact physician for next steps. Document details of situation and personnel involved.
Avoid Interruption of the Infusion	• In hospital, pausing infusion for < 15-30 minutes can allow for patient to shower, blood draw, or port reaccessing.[9] • Protocols for outpatient/home setting advise that the infusion should never be paused (except for port reaccessing).[9] • If interruption is needed, DO NOT FLUSH blinatumomab infusion line or IV catheter containing blinatumomab solution.[9] – Cancer Care Manitoba guidance: if accessing lumen, withdraw 2 mL of blood (containing drug) first, then flush.[12] • If the infusion interruption lasts ≥ 4 hours, hospitalization and dexamethasone may be necessary for re-initiation of blinatumomab. Always speak with the physician before re-initiating blinatumomab infusion.[4] • If blinatumomab must be stopped for an acute problem, infusion bag can be moved from central line to peripheral IV, but a newly prepared infusion bag is required to move from peripheral IV back to central line.[9]

Discontinuing Blinatumomab	• IMPORTANT: Do not flush blinatumomab infusion line or IV catheter containing blinatumomab solution. • Blinatumomab infusion may be discontinued for port needle change, toxicity or completed cycle.[4] **Discontinuation Procedure (guidance from University of Maryland Medical Centre)[4]** • Disconnect and aspirate 5 mL of blood from lumen to remove residual drug. • After aspiration, the lumen should be safe to flush. • Adequately flush catheter with 20 mL of 0.9% sodium chloride. • If flushing is difficult or if sluggish blood return is observed, consider use of clearing agent to prevent future occlusion (to be discussed with physician).

5. Safety Profile Overview

- Baseline assessment and monitoring guidance provided in the following sections aim to support proactive management of the potential toxicities associated with blinatumomab therapy.
- In addition to the common toxicities listed below, vigilance is required to manage less common but serious toxicities including Cytokine Release Syndrome, Tumour Lysis Syndrome, neurologic events (e.g., seizure, encephalopathy), and pancreatitis.

MOST COMMON ADVERSE REACTIONS

5.1: Most Common Adverse Reactions: MRD+ B-Cell Precursor Acute Lymphoblastic Leukemia[7]

- Common treatment-emergent adverse events (TEAEs) associated with blinatumomab therapy (occurring in ≥ 15%) in patients with MRD+ BCP-ALL (2 single-arm studies: N=137) included:

Toxicity	Any Grade	Grade ≥ 3	Toxicity	Any Grade	Grade ≥ 3
Pyrexia	91%	7%	Chills	28%	0%
Infusion-related reaction	77%	5%	Decreased immunoglobulins	18%	5%
Infection	39%	8%	Insomnia	18%	<1%
Headache	39%	4%	Rash	16%	<1%
Tremor	31%	4%	Neutropenia	15%	15%

Toxicities occurring in > 50% of patients | Toxicities occurring in 21-50% of patients | Toxicities occurring in ≤ 20% of patients

5.2: Most Common Adverse Reactions: Relapsed/Refractory B-Cell Precursor Acute Lymphoblastic Leukemia[7]

- Common treatment-emergent adverse events (TEAEs) associated with blinatumomab therapy (any grade occurring in ≥ 15%) in patients with relapsed/refractory BCP-ALL (TOWER study: N=267) included:

Toxicity	Any grade	Grade ≥ 3	Toxicity	Any Grade	Grade ≥ 3
Pyrexia	60%	7%	Neutropenia	23%	21%
Infection	43%	24%	Bacterial infectious disorders	21%	10%
Infusion-related reactions	34%	3%	Edema	17%	1%
Headache	29%	<1%	Hepatic enzymes increased	17%	10%
Anemia	27%	21%	Viral infectious disorders	16%	3%
Febrile neutropenia	24%	21%	Cough	15%	0%
Thrombocytopenia	24%	19%			

Toxicities occurring in > 50% of patients | Toxicities occurring in 21-50% of patients | Toxicities occurring in ≤ 20% of patients

6. Baseline Assessment

- Comprehensive laboratory testing is required prior to initiation of treatment.[1]
- Neurological examination is recommended for patients prior to and during treatment with blinatumomab.[7,11]
- Blinatumomab is not recommended for CD19-negative disease; assess CD19 expression at time of bone marrow testing.[7]
- Ensure patient can manage and self-monitor at home with appropriate caregiver/home support for outpatient component of therapy.

6.1: Suggested Parameters for Assessment at Baseline

Patient Assessment/ Physical Examination	Standard Laboratory Tests	Other Tests/Evaluations
• Neurological exam and history of neurologic events[7,11] – Some institutions include a writing test/signature log to be assessed (compared to baseline) by nurse every shift during nursing assessment[1] • Medication history – Review vaccination history[7] – Assess for drug interactions (i.e., drugs with narrow therapeutic window)[7] – Assess for drugs which may cause liver enzyme elevation[7]	• CBC with differential[11] • Liver function: ALT, AST, GGT, total blood bilirubin[7,11] • Renal function[7] • Electrolytes[11] • Pregnancy testing is recommended prior to treatment initiation in women of childbearing potential.	• Bone marrow blasts[7] • Peripheral blast count[7] • Immunophenotyping: CD19 expression – Blinatumomab not recommended in CD19-negative disease[7] • Cytogenetic analysis (detect abnormalities) – Identify patients at risk for AML lineage switch[7]

ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; CBC, complete blood count; GGT, gamma-glutamyl transferase

6.2: Other Patient Considerations Prior to Start of Blinatumomab

- Pregnancy and lactation
  - It is not known if blinatumomab can cause fetal harm or if it is present in human milk.[7]
  - Advise patients of childbearing potential to use effective contraception and discontinue nursing during and for a minimum of 48 hours after blinatumomab therapy.[7,11]
  - Regular pregnancy testing may be considered.
- Patients ≥ 65 years of age[7]
  - Elderly patients experienced a higher rate of neurologic events including cognitive disorder, encephalopathy, and confusion
- Serious infection
  - Patients > 65 years of age are at increased risk of infection.[7,13]
  - There has been limited experience using blinatumomab in patients with active infections.[7]

7. Drug Interactions

7.1: Drug Interaction Guidance

Immunization[7]
• The safety of live viral vaccines during or after blinatumomab has not been studied. • Vaccination with live vaccines is not recommended within the 2 weeks prior to initiating blinatumomab or during therapy. Live virus vaccines can be administered when B lymphocytes are within normal range following the last cycle of blinatumomab.
Drug-Drug Interactions
• No formal drug-drug interaction studies have been conducted with blinatumomab.[7] • Blinatumomab treatment-induced transient release of cytokines may suppress CYP450 enzymes.[7] • The highest risk for drug-drug interaction is within the first 9 days of cycle 1 and the first 2 days of cycle 2 in patients receiving concomitant CYP450 substrates, especially those with a narrow therapeutic index – e.g., warfarin, cyclosporine, tacrolimus (monitor and adjust dose as needed).[7] • Avoid non-steroidal anti-inflammatory drugs (NSAIDs) if possible as they may contribute to endothelial stress.[10]

8. Suggested Monitoring

8.1: Recommended Clinical Monitoring During Blinatumomab Treatment Course

	Cycle 1	Cycle 2	Cycle 3 and Beyond
Clinical Assessment Considering Syndromes and Conditions Below			
Infusion Reactions[7]	✓ Observe closely during first infusion of cycle	✓ Observe closely during first infusion of cycle	✓
Cytokine Release Syndrome (CRS) • Headache, pyrexia, hypotension, asthenia, nausea, total bilirubin increased, liver enzymes increased,[7] hypoxia[14]	✓ (Median onset 2 days)[7]	✓	✓
Disseminated Intravascular Coagulation (DIC) • Blood in urine or stool, bleeding near wound sites or from mouth, gums, or nose, bruising (small dots/large patches on body), chest pain, warmth, redness, pain and swelling of leg,[15] increased INR, decreased fibrinogen[16]	✓	✓	✓
Capillary Leak Syndrome (CLS) • Edema, hypotension, elevated hematocrit[17]	✓	✓	✓
Tumour Lysis Syndrome (TLS) • Monitor for signs and symptoms including renal function and fluid balance.[7,11] • Monitor blood levels of potassium, uric acid, phosphorus, calcium, creatinine (see Lab Tests below).[11]	✓ Closely monitor in first 48 hours	As clinically indicated	As clinically indicated
Infection signs and symptoms	✓	✓	✓
Neurologic events • Headache, tremor, encephalopathy, dizziness, convulsions, speech disorders, confusion, disorientation, altered consciousness, disturbances in coordination or balance, seizure activity[7]	✓ (Median time to first event within first 2 weeks)[7]	✓	✓
• Speech clarity, cognition/mentation, handwriting[4,10]	Assess once per shift	Assess once per shift	Assess once per shift
Pancreatitis • Abdominal pain/tenderness, nausea, vomiting[7]	✓	✓	✓
Lab Tests			
CBC[11] (with differential; including WBC, ANC, hematocrit, INR, fibrinogen)[16]	✓	✓	Once weekly* and as clinically indicated
Liver function (ALT, AST, GGT, total bilirubin)[7]	✓	✓	Once weekly* and as clinically indicated
Renal function (creatinine)[11]	✓	✓	Once weekly* and as clinically indicated
Calcium[7]	✓	As clinically indicated	Once weekly* and as clinically indicated
Potassium[7]	✓	As clinically indicated	Once weekly* and as clinically indicated
Phosphorus[7]	✓	As clinically indicated	Once weekly* and as clinically indicated
Uric acid[7]	✓	As clinically indicated	Once weekly* and as clinically indicated

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CBC, complete blood count; GGT, gamma-glutamyl transferase; INR, international normalized ratio; WBC, white blood cell count
*Expert Opinion

8.2: Hospital Visit and Readmission Guidance for Patients Receiving Blinatumomab in the Home Setting

- Home healthcare should include weekly hospital visits.[10]
- Reasons for readmission may include infections, fever, drug-related toxicity requiring in-patient monitoring and management.[1]
- If the blinatumomab infusion has been interrupted for ≥ 4 hours (for pump error, toxicity, etc.), hospital readmission is recommended to re-initiate treatment with appropriate premedication (refer to tables 3.2 and 3.4 for MRD+ and relapsed or refractory (R/R) guidance, respectively).[1,4,7]

9. Adverse Reaction Management

- Specific guidance follows (pages 12-16) for:
  - Cytokine Release Syndrome
  - Tumour Lysis Syndrome
  - Neurologic Events
  - Pancreatitis
  - Neutropenia/Serious Infection

DOSE MODIFICATION GUIDANCE

- Specific guidance follows for Cytokine Release Syndrome, Tumour Lysis Syndrome, Neurologic Events, Pancreatitis, and Neutropenia/Serious Infection
- Other clinically relevant adverse reactions should be managed as follows:[7]

9.1: Dose Modifications for Grade 3 and Grade 4 Adverse Reactions

Grade 3 (Severe) Adverse Reactions (Patients ≥ 45 kg)	• Interrupt blinatumomab until ≤ Grade 1 (mild). • Restart blinatumomab at 9 mcg/day; escalate to 28 mcg/day after 7 days if the toxicity does not recur. • If the toxicity takes > 14 days to resolve, discontinue blinatumomab permanently.
Grade 4 (Life-Threatening) Adverse Reactions (Patients ≥ 45 kg)	• Consider discontinuing blinatumomab permanently.

For patients weighing < 45kg, please refer to the BLINCYTO Product Monograph.[7]

9.2: Dose Modifications for Hepatic Enzyme Elevations

Increased Hepatic Enzymes[7]	• Majority observed within the first week of initiating treatment and did not require treatment interruption or discontinuation. • Monitor ALT, AST, GGT and total blood bilirubin prior to start and during blinatumomab therapy, especially for patients receiving other drugs known to be associated with increased liver enzymes. • Interrupt treatment if transaminases rise > 5 x ULN or if bilirubin rises > 3 x ULN.

ALT, alanine transferase; AST, aspartate transferase; GGT, gamma-glutamyl transferase; ULN, upper limit of normal

- If the blinatumomab infusion is interrupted ≤ 7 days due to an adverse event, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption[7]
- If the blinatumomab infusion is interrupted > 7 days due to an adverse event, start a new cycle[7]

CYTOKINE RELEASE SYNDROME (CRS)

	Frequency[7]			
	MRD+ B-Cell Precursor ALL (2 Single-arm studies, N=137)		Relapsed/Refractory B-Cell Precursor ALL (TOWER STUDY, N=267)	
	Any	Grade ≥ 3	Any	Grade ≥ 3
Cytokine Release Syndrome	Not reported	Not reported	14%	3%
Infusion-related Reactions	77%	5%	34%	3%

Description

- CRS is a systemic inflammatory response observed with blinatumomab; median time to onset of CRS in clinical trials was 2 days.[7]
- Most often flu-like symptoms are experienced.[4]
- Serious adverse events that may be associated with CRS include asthenia, pyrexia, headache, hypotension, elevation of liver enzymes (AST and ALT), total bilirubin increased, and nausea.[7]
- Severe and fatal CRS has occurred in patients receiving blinatumomab.[7]
- CRS has been commonly associated with Capillary Leak Syndrome (CLS) and Disseminated Intravascular Coagulation (DIC).[7]
- In the context of CRS, hemophagocytic histiocytosis/macrophage activation syndrome (MAS) has been uncommonly reported.[7]
- Infusion reactions include hypotension, hypertension, fever, myalgia, tachypnea, face swelling and rash.[1]
  - Infusion reactions may be clinically indistinguishable from CRS manifestations[7]

Proactive Measures

- Accidental bolus administration of blinatumomab can cause CRS; to prevent this, the infusion should run through a dedicated catheter and the catheter should NOT be flushed during drug infusion.[4]
- The pump should be checked by two healthcare professionals (e.g., registered nurses) when programmed to ensure correct infusion rate.

PREMEDICATION

- Recommendations for adult MRD+ ALL:[7]
  - Prednisone 100 mg equivalent (e.g., dexamethasone 16 mg) IV 1 hour prior to blinatumomab on day 1 of each cycle.
- Recommendations for adult R/R ALL:[7]
  - Dexamethasone 20 mg IV 1 hour prior to blinatumomab on day 1 of each cycle.[7]
  - Consider dexamethasone prior to dose escalation and prior to re-initiation if treatment was interrupted for ≥ 4 hours.*[1,4,8]
  - If high tumour burden (≥ 50% of leukemic blasts in bone marrow or > 15 x 10^9/L peripheral blood leukemic blast count), dexamethasone (not to exceed 24 mg/day) for up to 4 days prior to first dose of blinatumomab.

STANDING ORDERS

- Consider standing orders for as-needed dexamethasone (and tocilizumab per institutional CRS guidelines) for prompt treatment of CRS.[4]

MONITORING

- Closely observe for infusion reactions, especially first infusion of cycles 1-2.[7]
- Monitor liver enzymes (AST, ALT, GGT) and total bilirubin prior to start of blinatumomab therapy and during treatment.[7]
- Monitor patients for signs and symptoms of CLS and DIC:[7]
  - CLS: edema, hypotension, elevated hematocrit.[17]
  - DIC: blood in urine or stool, bleeding near wound sites or from mouth, gums or nose, bruising, chest pain, warmth, redness, pain and swelling of leg[15]; low platelet count, prolonged clotting time.

Patient Education

- Educate patients to report signs and symptoms of CRS and infusion reactions: fever, weakness/tiredness, headache, dizziness, low blood pressure, vomiting, nausea, chills, face swelling, skin rash, and trouble breathing/wheezing.[8]
- Educate patients to report signs and symptoms of CLS and DIC (above)

Toxicity Management (Patients ≥ 45kg)†

Any Grade CRS[4]

- Provide vigilant supportive care.
- Assess for tumour lysis.
- Obtain cultures and empirically treat infection.

Grade 3 (Severe) CRS

- Interrupt blinatumomab until ≤ Grade 1 (mild).[7]
- Treat with dexamethasone 8 mg (PO or IV) every 8 hours for up to 3 days; then taper over 4 days.[8]
- Once resolved to ≤ Grade 1 (mild), restart blinatumomab at 9 mcg/day; escalate to 28 mcg/day after 7 days if the toxicity does not recur.[7,8]

Grade 4 (Life-threatening) CRS

- Discontinue blinatumomab permanently.[7]
- Treat with dexamethasone 8 mg (PO or IV) every 8 hours for up to 3 days (orally or IV); then taper over 4 days.[8]

Additional treatment if necessary:

- If no improvement following drug cessation and steroid treatment, consider tocilizumab (IL-6 receptor inhibitor) per institutional CRS guidelines.[18]
  - Avoid tocilizumab in patients with serious CNS toxicities.[4]

Toxicities occurring in > 50% of patients | Toxicities occurring in 21-50% of patients | Toxicities occurring in ≤ 20% of patients

ALT, alanine transferase; AST, aspartate transferase; GGT, gamma-glutamyl transferase

*Recommended in US Prescribing Information,[8] not Health Canada-approved. †See BLINCYTO Product Monograph for toxicity management guidance for patients < 45 kg.

See following page for CTCAE grading of CRS and infusion-related reactions.

CTCAE Grade[19]	1	2	3	4
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated

TUMOUR LYSIS SYNDROME (TLS)

	Frequency[7]			
	MRD+ B-Cell Precursor ALL (2 Single-arm studies, N=137)		Relapsed/Refractory B-Cell Precursor ALL (TOWER STUDY, N=267)	
	Any	Grade ≥ 3	Any	Grade ≥ 3
Tumour Lysis Syndrome	Not reported	Not reported	4%	3%

Description

- TLS is caused by the release of cellular components into the blood following the breakdown of many dying cancer cells.
- Severe, life-threatening or fatal TLS has occurred in patients receiving blinatumomab.[7]
- A higher incidence of TLS was reported in clinical studies for patients with moderate renal impairment (CrCl 30 to < 60 mL/min) compared to patients with mild impairment or normal renal function.[7]

Proactive Measures

- Prophylactic measures recommended to prevent TLS during blinatumomab treatment, especially for patients with a high tumour burden or higher leukocytosis:[7]
  - Leukoreduction with steroids prior to initiating blinatumomab
  - Aggressive hydration
  - Antihyperuricemic therapies (allopurinol or rasburicase)
- Monitor patients closely for TLS signs and symptoms, renal function, electrolytes, and fluid balance in the first 48 hrs following the first infusion.[7]

Patient Education

- Advise patients to monitor themselves for signs and symptoms of tumour lysis syndrome:[20]
  - Nausea with/without vomiting
  - Fatigue, lack of appetite
  - Muscle spasms and cramps
  - Reduced urine output, dark urine, flank pain
  - Heart palpitations

Toxicity Management (Patient ≥ 45kg)*

Grade 3 (Severe) TLS

- Interrupt blinatumomab until ≤ Grade 1 (mild).[7]
- Restart blinatumomab at 9 mcg/day; escalate to 28 mcg/day after 7 days if the toxicity does not recur.[7]
- If the toxicity takes > 14 days to resolve, discontinue blinatumomab permanently.[7]

Grade 4 (Life-threatening) TLS

- Consider permanent discontinuation of blinatumomab.[7]

Toxicities occurring in > 50% of patients | Toxicities occurring in 21-50% of patients | Toxicities occurring in ≤ 20% of patients

CrCl, creatinine clearance.

*See BLINCYTO Product Monograph for toxicity management guidance for patients < 45 kg.

CTCAE Grade[19]	1	2	3	4
Tumour lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated

NEUROLOGIC EVENTS

	Frequency[7]			
	MRD+ B-Cell Precursor ALL (2 Single-arm studies, N=137)		Relapsed/Refractory B-Cell Precursor ALL (TOWER STUDY, N=267)	
	Any	Grade ≥ 3	Any	Grade ≥ 3
Headache	39%	4%	29%	<1%
Tremor	31%	4%	10%	<1%
Aphasia	12%	<1%	1%	<1%
Dizziness	10%	<1%	7%	<1%
Encephalopathy	10%	4%	1%	1%
Seizure	Not reported*	Not reported*	2%	1%

Description

General Neurologic Events

- Neurologic events of any grade occurred in ~50% of adult patients; median time to onset was within the first 2 weeks and majority of events resolved.[7]
- Grade ≥ 3 (severe, life-threatening and fatal) neurologic events have occurred in patients receiving blinatumomab, including:[7]
  - Speech disorders, seizures, encephalopathy, confusion and disorientation, disturbances in consciousness, and coordination and balance disorders.
- Elderly patients (≥ 65 years of age) experienced a higher rate of neurologic AEs (confusion, encephalopathy and cognitive disorder).[7]
- There is limited experience with blinatumomab in patients with active ALL in the CNS or a history of neurologic events.[7]
- Prior neurological events have been associated with a higher risk of neurological toxicity.[18]

Leukoencephalopathy

- Cranial MRI changes indicative of leukoencephalopathy have been observed in patients receiving blinatumomab.[7]
  - Especially if prior cranial irradiation and anti-leukemic chemotherapy (including systemic high dose methotrexate or intrathecal cytarabine).[7]
  - Clinical significance of cranial MRI changes is unknown.[7]

Proactive Measures

- Perform a neurological examination prior to initiating blinatumomab and clinically monitor for neurologic signs and symptoms.[7]
  - Headache, tremor, encephalopathy, dizziness, convulsions, speech disorders, confusion, disorientation, altered consciousness, disturbances in coordination or balance, seizure activity.[7]
- Given potential for progressive multifocal leukoencephalopathy (PML), monitor patients for signs and symptoms.[7]
- Assess the following at least once per shift during blinatumomab therapy:
  - Speech clarity changes.
  - Cognition and/or mentation changes.
  - Consider storing signature log in patient's chart to monitor for changes in patient's ability to hand-write a pre-specified statement (compared to baseline).[4,10]

Patient Education

- Advise patients to self-monitor for signs and symptoms of neurological problems:
  - Difficulty communicating, skin tingling, seizure, tremors, difficulty remembering, difficulty thinking/processing thoughts.[7,18]
- Advise patients to self-monitor for signs and symptoms of PML:
  - Progressive weakness and speech, visual or personality changes.[21]
- Due to the potential for neurologic events and risk of losing consciousness, advise patients to refrain from driving and engaging in hazardous occupations/activities (e.g., operating heavy/potentially dangerous machinery).[7]

Toxicity Management (Patient ≥ 45kg)†

Seizure

- If > 1 seizure occurs, permanently discontinue blinatumomab.[7]
- Consider appropriate secondary prophylaxis or supportive treatment (e.g., anti-epileptics for seizures).[7,18]

Leukoencephalopathy

- If suspected, consider consultation with a neurologist, CSF examination and brain MRI.[7]
- If confirmed, discontinue blinatumomab.[11]

Grade 3

- Interrupt blinatumomab until ≤ Grade 1 (mild) and for ≥ 3 days.[7]
- Restart blinatumomab at 9 mcg/day; escalate to 28 mcg/day after 7 days if the toxicity does not recur.[7]
  - For re-initiation, premedicate with dexamethasone (up to 24 mg) with a 4-day taper.[7]
- As secondary prophylaxis, consider appropriate anticonvulsant medication.[7]
- If the toxicity occurred at 9 mcg/day, or if the toxicity takes > 7 days to resolve, discontinue blinatumomab permanently.[7]

Grade 4

- Discontinue blinatumomab permanently.[7]

Other Treatment Options

- Severe symptoms (e.g., encephalopathy or aphasia):[18]
  - Steroids (dexamethasone).[4,18]

Toxicities occurring in > 50% of patients | Toxicities occurring in 21-50% of patients | Toxicities occurring in ≤ 20% of patients

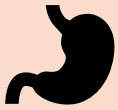
*Seizure (any grade) was reported in 3% of subjects in the BLAST study.[6] †See BLINCYTO Product Monograph for toxicity management guidance for patients < 45 kg.
CSF, cerebral spinal fluid; MRI, magnetic resonance imaging

See following page for CTCAE grading of neurologic adverse events.

CTCAE Grade[19]	1	2	3	4
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-
Dysphasia (Aphasia)	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures

ADL, activities of daily living

PANCREATITIS



	Frequency			
	MRD+ B-Cell Precursor ALL (2 Single-arm studies, N=137)		Relapsed/Refractory B-Cell Precursor ALL (TOWER STUDY, N=267)	
	Any	Grade ≥ 3	Any	Grade ≥ 3
Pancreatitis	Not reported	Not reported	Not reported	0.4%[5]

Description

- Severe, life-threatening, or fatal pancreatitis has occurred in patients receiving blinatumomab in clinical trials and the post-market setting.[7]
- Signs and symptoms of pancreatitis: upper abdominal pain accompanied with vomiting, nausea, or abdominal tenderness.[7]
- High-dose steroid therapy may contribute to the risk of pancreatitis.[7]

Proactive Measures

- Routinely assess for sign and symptoms of pancreatitis.
-

Patient Education

- Educate patients to report signs and symptoms of pancreatitis: abdominal tenderness, pain in stomach/abdomen with/without vomiting and nausea.[7]

Toxicity Management (Patient ≥ 45kg)*

- Evaluate patients with pancreatitis signs and symptoms.[7]
- If pancreatitis is suspected, temporarily interrupt or discontinue blinatumomab treatment according to recommendations below.[7]

Grade 3

- Interrupt blinatumomab until Grade ≤ 1; restart at 9 mcg/day and escalate to 28 mcg/day after 7 days if toxicity does not recur.[7]
- If toxicity takes > 14 days to resolve, permanently discontinue blinatumomab.[7]

Grade 4

- Consider permanently discontinuing blinatumomab.[7]

*See BLINCYTO Product Monograph for toxicity management guidance for patients < 45 kg.

CTCAE Grade[19]	1	2	3	4
Pancreatitis	-	Enzyme elevation or radiologic findings only	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated

NEUTROPENIA/SERIOUS INFECTION

	Frequency[7]			
	MRD+ B-Cell Precursor ALL (2 Single-arm studies, N=137)		Relapsed/Refractory B-Cell Precursor ALL (TOWER STUDY, N=267)	
	Any	Grade ≥ 3	Any	Grade ≥ 3
Neutropenia	15%*	15%*	23%†	21%†
Febrile Neutropenia	Included above	Included above	24%	21%
Infections – pathogens unspecified	39%	8%	43%	24%

Description

Neutropenia and Febrile Neutropenia

- Life-threatening cases of neutropenia have occurred in patients receiving blinatumomab.[7]

Serious Infection

- There is limited experience with blinatumomab in patients with active uncontrolled infections.[7]
- Patients ≥ 65 years of age are at increased risk of infection.[7,13]
- Serious and/or fatal infections in patient receiving blinatumomab have included: sepsis (e.g., *Escherichia* sepsis) and septic shock, bacteremia (e.g., *Enterococcal* bacteremia), pneumonia (bronchopneumonia, fungal pneumonia), lung infection, opportunistic infections (e.g., *Aspergillus, Candida*, *Fusarium*), catheter site infections.[7]

Proactive Measures

- Monitor laboratory parameters (including white blood cell count and absolute neutrophil count) during blinatumomab infusion; treat as appropriate.[7]
- Monitor patients for infection signs and symptoms, treat as appropriate.[7]
- Assess for device-related infection[7] and manage as appropriate.

Patient Education

- Educate patients on the potential for neutropenia and severe infection, and the importance of blood tests.
- Advise patients to monitor themselves for signs and symptoms associated with infection (fever, aches, feeling tired, cough).[7]
- Instruct patients to inform healthcare team immediately if they develop a fever and/or have signs of infection.[10]
- Educate patients on how to keep catheter/injection site clean.[7]

Toxicity Management (Patient ≥ 45kg)‡

- If febrile neutropenia is suspected, perform infectious work up:
  - Collect blood and urine cultures, swabs for respiratory viruses (e.g., covid, influenza, RSV) for analysis.
  - Imaging as clinically indicated (e.g., rule out pneumonia).
- Manage febrile neutropenia with broad spectrum antibiotics and intensive care support as necessary.[22]
- Temporary interruption or discontinuation of blinatumomab may be required to manage infections (see below).[7]

Grade 3

- Interrupt blinatumomab until Grade ≤ 1; restart at 9 mcg/day and escalate to 28 mcg/day after 7 days if toxicity does not recur.[7]
- If toxicity takes > 14 days to resolve, permanently discontinue blinatumomab.[7]

Grade 4

- Consider permanently discontinuing blinatumomab.[7]

Toxicities occurring in > 50% of patients | Toxicities occurring in 21-50% of patients | Toxicities occurring in ≤ 20% of patients

*Includes neutropenia, febrile neutropenia and neutrophil count decreased.
†Includes neutropenia and neutrophil count decreased.
‡See BLINCYTO Product Monograph for toxicity management guidance for patients < 45 kg.

CTCAE Grade[19]	1	2	3	4
Febrile neutropenia	-	-	ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour	Life-threatening consequences; urgent intervention indicated
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000 - 500/mm^3; <1.0 - 0.5 x 10^9 /L	<500/mm^3; <0.5 x 10^9 /L

ANC, absolute neutrophil count; LLN, lower limit of normal

10. Multidisciplinary Communication

- Multidisciplinary communication is essential to prevent blinatumomab medication errors, reduce the risk of adverse events and avoid wasting drug.
- Distinct order sets can help direct safe and appropriate use including admission orders; cycle 1 orders, subsequent cycle orders, and readmission in midcycle orders; these should clearly identify the appropriate dose, rate of infusion, premedications, and preparation instructions.[1]
- To ensure best practices are followed, add critical information to the electronic medical record and/or order sets:[4]
  - Baseline and monitoring assessments
  - Dexamethasone premedication recommendations
  - Signs/symptoms of CRS, neurotoxicity
  - Guidance for adverse events (e.g., communication and supportive care strategies, standing orders for as-needed medications)
- Transitioning to outpatient care requires careful planning and coordination to avoid dose interruptions and drug waste.[4]
- It is important to establish the roles and responsibilities of multidisciplinary team members for outpatient and home transition.

10.1: Suggested Responsibilities for Multidisciplinary Team Members

Multidisciplinary Team Member	Recommended Responsibilities
Nurse	• Lead/support multidisciplinary team education and development of order sets for blinatumomab delivery.[1] • Communicate patient's treatment response, medication administration timing, status of access device in shift report.[1] • At each shift, document neurological status.[1] – Patient's daily signature log, neurological checks, presence/absence of seizure activity • Immediately report any changes in patient's status to prescriber for guidance.[1] – Neurological status, laboratory results, vitals • Mark IV infusion lines with "Do Not Flush" stickers to remind all staff.[1] • Use CTCAE grading to clearly and concisely inform on-call prescriber of adverse events.[1] • Coordinate treatment schedule with pharmacy to avoid wasting blinatumomab.[1] – Ensure appropriate handling and storage of blinatumomab – Inform pharmacy of treatment schedule delays or changes • Explain communication requirements between patient and outpatient care providers.[4] • Coordinate pump/bag change from hospital to outpatient supply and educate patient/caregiver on infusion pump, treatment and monitoring before patient is discharged.[1,9] – Double check infusion pump programming and infusion line installation/connection from bag to catheter before patient leaves outpatient oncology clinic.
Pharmacist	• Lead/support multidisciplinary team education and development of order sets for blinatumomab delivery[1] • Coordinate with nursing to minimize drug waste and initiate infusion during daytime to enable outpatient transition.[1] • Communicate and collaborate with nursing in cases of treatment schedule delays or changes.[1] • Provide drug stability information and "refrigerate" sticker on blinatumomab bag to ensure appropriate storage if not infused immediately.[1] • Monitor and maintain blinatumomab inventory.[1]
Physician (or Advanced Practice Nurse)	• Make decisions related to:[1] – Infusion duration, hospitalization/outpatient planning – Dose adjustments, interruptions, or discontinuation (due to toxicities, vital signs, laboratory results and clinical status) – IV catheter maintenance • Communicate any changes to treatment plan to other clinical team members.[1] • Ensure appropriate co-medications are prescribed for in-hospital and outpatient/home settings (e.g., intrathecal chemotherapy, dexamethasone/prednisone, antihyperuricemic).
Case Manager	• Work with nurse and physician (or advanced practice nurse) to organize outpatient infusion.[1] • Coordinate patient, caregivers, and healthcare team members to facilitate transition to outpatient/home care.[1]
Outpatient Infusion Team	• Provide contact information to serve as a resource for patients at home if patient has questions or if toxicities arise.[1] • Ensure the infusion bag is changed in the outpatient setting at the same time each day per chosen infusion duration.[9] – Follow directions regarding administration of co-medications, blood draws, IV catheter care • Instruct patient to visit outpatient oncology clinic or emergency department if an infusion pump problem cannot be fixed.[9] – Call oncology clinic or on-call oncologist for any concerns

11. Checklist: Patient Education

Note: ensure patient's caregiver is present for education session

- ☐ Type of treatment and treatment goal
  - Blinatumomab is a type of immunotherapy called a bispecific T-cell engager (BiTE).
  - Blinatumomab helps the immune system destroy a particular type of white blood cell present in acute lymphoblastic leukemia.
- ☐ How blinatumomab is administered
  - Blinatumomab is administered by continuous intravenous (IV) infusion using an infusion pump for 4 weeks, followed by 2 weeks off therapy.
  - The infusion is given in-hospital initially, but following the in-hospital period, infusion can be given in an outpatient setting if the patient is stable and sufficient support is available at home.
- ☐ Care of catheter/infusion site and pump
  - How to keep catheter/infusion site clean
  - Prior to discharge and transition to outpatient care:[13]
    - Advise patients not to change the pump settings
    - Educate patients about pump troubleshooting
    - Provide contact information in cases of pump error and to immediately alert healthcare team if malfunction occurs.
- ☐ Signs and symptoms of serious side effects and importance of reporting these to the healthcare team
  - Cytokine release syndrome and infusion reactions (e.g., fever, weakness, headache, chills, swelling, difficulty breathing, rash, signs of bleeding)
  - Tumour lysis syndrome (e.g., muscle spasm, cramps, reduced urine output, dark urine, flank pain, palpitations)
  - Neurologic side effects (e.g., shaking, dizziness, drowsiness, speech changes, skin tingling, confusion)
  - Pancreatitis (e.g., abdominal pain/tenderness, nausea, vomiting)
  - Severe infections (e.g., fever, aches, feeling tired, cough, catheter/device site pain or redness)
- ☐ Other medications
  - Medications used to reduce the risk of serious side effects
  - Consult healthcare team regarding timing of vaccinations
  - Potential for drug interactions, importance of disclosing all medications patient is taking
- ☐ Fertility, pregnancy, and breastfeeding warnings (for patients of childbearing potential)
  - The effect of blinatumomab on a human fetus is unknown.
  - Use effective contraception and discontinue nursing for a minimum of 48 hours after treatment.
- ☐ Available social support services

12. Acronyms and Abbreviations

ADL, activities of daily living
AE, adverse event
ALL, acute lymphoblastic leukemia
ALT, alanine transferase
AML, acute myeloid leukemia
ANC, absolute neutrophil count
AST, aspartate transferase
BCP-ALL, B-cell precursor acute lymphoblastic leukemia
BiTE, bispecific T-cell engager
BSA, body surface area
CBC, complete blood count
CD19, cluster of differentiation 19
CD3, cluster of differentiation 3
CIV, continuous intravenous infusion
CLS, capillary leak syndrome
CNS, central nervous system
CR, complete remission
CrCl, creatinine clearance
CRh, complete remission with partial hematologic recovery
CRS, cytokine release syndrome
CSF, cerebral spinal fluid
CTCAE, common terminology criteria for adverse events
CYP2C9, cytochrome P450 2C9
CYP3A4, cytochrome P450 3A4
CYP450, cytochrome P450
DEHP, di-ethylhexyl phthalate
DIC, disseminated intravascular coagulation
EVA, ethyl vinyl acetate
ECOG-PS, European Cooperative Oncology Group – Performance Status
GGT, gamma-glutamyl transferase
GI, gastrointestinal
HCP, healthcare professional
HSCT, hematopoietic stem cell transplant
IL-6, interleukin-6
INR, international normalized ratio
IV, intravenous
LLN, lower limit of normal
MAS, macrophage activation syndrome
MRD, minimal residual disease
MRI, magnetic resonance imaging
NOC/c, Notice of Compliance with conditions
NSAID, non-steroid anti-inflammatory drug
PICC, peripherally inserted central catheter
PML, progressive multifocal leukoencephalopathy
PVC, polyvinyl chloride
R/R, relapsed or refractory
RSV, Respiratory syncytial virus
SOC, standard of care
TEAE, treatment-emergent adverse event
TLS, tumour lysis syndrome
ULN, upper limit of normal
WBC, white blood cell count

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