CANO ACIO
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 February 4, 2028.

Quick Reference Guide: Blinatumomab Continuous Infusion for Adult Patients with B-Cell Precursor Acute Lymphoblastic Leukemia

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Key Points

TREATMENT OVERVIEW & ADMINISTRATION

Blinatumomab infusion
- Delivered as a 28-day continuous IV infusion at a constant flow rate using an infusion pump, followed by a 14-day treatment-free interval.[1]
- Dosing and timing of course of therapy depend on indication.[1]

Hospitalization
- Recommended for **starts of cycles 1 and 2** to monitor and manage toxicities.[1]

Co-medications
- **Premedication** with steroids and **intrathecal chemotherapy CNS prophylaxis** are recommended.[1]

Administration
- **In-line filters:** Use a low protein-binding 0.2 or 0.22 micron in-line filter; do not use an in-line filter with a 7-day infusion bag.[1]
- Use a **dedicated line** for blinatumomab.[1]
- Prior to starting the infusion on day 1, ensure **catheter patency**
- **Do not flush the blinatumomab infusion line containing blinatumomab solution.**[1a]
- **Do not infuse the bag overfill** (do not empty infusion bag).[2]
- **Change infusion bag at the same time each day**, according to the chosen infusion duration, independent of the remaining volume.[2]

[a]Refer to **page 4 (catheter patency & occlusion section)** for more guidance on flushing of blinatumomab infusion lines.

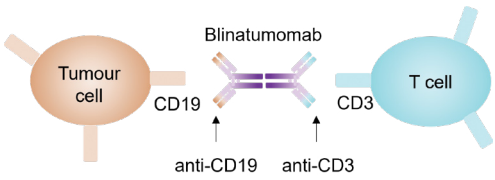
ADVERSE EVENT MONITORING & MANAGEMENT

Serious warnings and precautions
- Include cytokine release syndrome (CRS), tumour lysis syndrome (TLS), neurologic events including immune effector cell-associated neurotoxicity (ICANS), neutropenia/serious infection, and pancreatitis.[1]
- Monitor patients to allow for early detection of adverse events.[1]
- Proactively identify institutional protocols for CRS, neurotoxicity, and ICANS, and applicability to patients receiving blinatumomab.

Cytokine release syndrome (CRS)
- **Accidental bolus administration** of blinatumomab can cause CRS or contribute to TLS.[2]
- **Median time to onset:** 2 days.[1]
- **Infusion reactions** may be clinically indistinguishable from CRS manifestations; assess and monitor patients carefully.[3]
- **Educate patients to recognize and report signs and symptoms** of CRS, capillary leak syndrome (CLS), and disseminated intravascular coagulation (DIC).

Neurotoxicity and ICANS
- **The ICE score** is a tool for assessing and grading ICANS.[4]
- **Educate patients to recognize and report signs and symptoms** of neurotoxicity and ICANS.

Tumour lysis syndrome (TLS)
- Monitor patients closely for **TLS signs and symptoms, including renal function, electrolytes, and fluid balance**, in the first 48 hours following the first infusion.[1]
- Ensure the patient is on appropriate TLS prevention **during the first cycle**.[1]



MECHANISM OF ACTION
- Blinatumomab is an immunotherapeutic agent called a bispecific T-cell engager (BiTE®).[5]
- BiTE® therapies engage the patient's own immune system and facilitate binding of T-cells to tumour cells, which leads to tumour cell lysis.[5]
- Blinatumomab is rapidly eliminated due to its short half-life (2.20 hours).[1]

HEALTH CANADA INDICATIONS: ADULT BCP-ALL[1]

BCP-ALL	• Patients with Philadelphia chromosome (–) CD19+ BCP-ALL in the consolidation phase of multiphase chemotherapy.
MRD+ BCP-ALL	• Patients with Philadelphia chromosome (–) CD19+ BCP-ALL in first or second hematologic complete remission with minimal residual disease (MRD) ≥ 0.1%. Patients are to be selected for treatment based on detection of MRD as determined by an accredited laboratory using validated assay methods.
Relapsed or Refractory BCP-ALL	• Adult patients with Philadelphia chromosome (–) relapsed or refractory BCP-ALL.

Treatment Overview

- **Co-medication:** For all indications, intrathecal chemotherapy prophylaxis is recommended before and during blinatumomab therapy to prevent CNS ALL relapse.[1]
- **Administration:** Blinatumomab is administered as a continuous intravenous infusion, delivered at a constant flow rate using an infusion pump.[1]
- **Dosing** for patients ≥ 45 kg is shown below; refer to the Product Monograph for patients < 45 kg.[1]

1 BCP-ALL in Consolidation Phase of Multiphase Chemotherapy[1]

Recommendation	Cycle 1: Consolidation (42 days)	Cycle 2: Consolidation (42 days)	Subsequent cycles (42 days/cycle)
Hospitalization	**First 3 days**	**First 2 days**	HCP supervision or hospitalization for cycle starts and re-initiations
Premedication	**Dexamethasone** 20 mg IV within 1 hour prior to the first dose of blinatumomab of each cycle		
Blinatumomab dose	Days 1–28: 28 mcg/day		
Treatment-free interval	Days 29–42 (14 days)		

Course of therapy: Patients may receive 4 cycles of blinatumomab monotherapy incorporated into the consolidation phase of multiphase chemotherapy

Blinatumomab (42 days/cycle), 4 cycles used intermittently in consolidation, each cycle as follows:	
Days 1–28	**Days 29–42**
Blinatumomab	–

2 MRD+ BCP-ALL[1]

Recommendation	Cycle 1: Induction (42 days)	Cycle 2: Consolidation (42 days)	Cycles 3–4: Consolidation (42 days/cycle)
Hospitalization	**First 3 days**	**First 2 days**	HCP supervision or hospitalization for cycle starts and re-initiations
Premedication	**Prednisone** 100 mg IV or equivalent (e.g., dexamethasone 16 mg) 1 hour prior to the first dose of blinatumomab of each cycle		
Blinatumomab dose	Days 1–28: 28 mcg/day	Days 1–28: 28 mcg/day	Days 1–28: 28 mcg/day
Treatment-free interval	Days 29–42 (14 days)	Days 29–42 (14 days)	Days 29–42 (14 days)

Course of therapy: Patients may receive 1 cycle of blinatumomab as induction treatment followed by 3 additional cycles of blinatumomab as consolidation treatment

Cycle 1: Induction		Cycle 2: Consolidation		Cycle 3: Consolidation		Cycle 4: Consolidation	
Days 1–28	Days 29–42	Days 1–28	Days 29–42	Days 1–28	Days 29–42	Days 1–28	Days 29–42
Blinatumomab	–	Blinatumomab	–	Blinatumomab	–	Blinatumomab	–

3 Relapsed or Refractory BCP-ALL[1]

Recommendation	Cycle 1: Induction (42 days)	Cycle 2: Induction (42 days)	Cycles 3, 4, 5: Consolidation (42 days/cycle)	Up to 4 cycles (cycles 6, 7, 8, 9): Maintenance (84 days/cycle)
Pre-phase treatment	**If high tumour burden,[a] dexamethasone** (not > 24 mg/day) for up to 4 days prior to first dose of blinatumomab is recommended			
Hospitalization	**First 9 days**	**First 2 days**	HCP supervision or hospitalization for cycle starts	
Premedication	**Dexamethasone** 20 mg IV 1 hour prior to the first dose of blinatumomab[b]			
Blinatumomab dose	• Days 1–7: 9 mcg/day • Days 8–28: 28 mcg/day	Days 1–28: 28 mcg/day	Days 1–28: 28 mcg/day	Days 1–28: 28 mcg/day
Treatment-free interval	Days 29–42 (14 days)	Days 29–42 (14 days)	Days 29–42 (14 days)	Days 29–84 (56 days)

Course of therapy: Patients may receive 2 cycles of blinatumomab as induction treatment followed by 3 additional cycles of blinatumomab as consolidation treatment, and up to 4 cycles of blinatumomab as maintenance therapy

Cycles 1 and 2		Cycles 3, 4, 5		Up to 4 cycles (cycles 6, 7, 8, 9)	
Induction		Consolidation		Maintenance	
Days 1–28	Days 29–42	Days 1–28	Days 29–42	Days 1–28	Days 29–84
Blinatumomab	–	Blinatumomab	–	Blinatumomab	–

[a] ≥ 50% leukemic blasts in bone marrow or > 15 x 10^9/L peripheral blood leukemic blast count.
[b] For cycle 1, consider premedication with dexamethasone prior to dose escalation and re-initiation if treatment was interrupted for ≥ 4 hours, per recommendation in US Prescribing Information.[6]

Administration: Key Points

✓	**Prior to starting infusion on day 1, ensure catheter patency.**[2] • On day 1 only: prior to initiation, ensure catheter has a brisk blood return (can aspirate ≥ 3 mL in ≤ 3 seconds) and flushes easily.[2]

✓	**Change the infusion bag at the same time each day, according to the chosen infusion duration, independent of remaining volume.**[2]
	• The timing of blinatumomab infusion initiation on day 1 of a cycle should consider[7]:
	  • When there are sufficient resources to monitor and address any toxicities or questions.
	  • The timing for outpatient administration, given the requirement for precise timing of IV bag changes.

✗	**Do <u>not</u> flush the blinatumomab infusion line, especially when changing infusion bags.**[1] • Flushing when changing bags or at completion of infusion can result in excess dosage and complications (e.g., CRS, ICANS, TLS).[1]
✗	**Do <u>not</u> infuse blinatumomab bag overfill.**[2] • At the end of the infusion, dispose of any unused blinatumomab solution in the IV bag and tubing in accordance with local requirements.[1]

Infusion Pump Set-up

Bags and Tubing[1]	Filter[1]	Infusion Pump	Vascular Access
• Blinatumomab is **incompatible** with DEHP. • Use polyolefin, DEHP-free PVC, or EVA infusion bags and IV tubing sets.	• **24-hr, 48-hr, 72-hr, and 96-hr infusions:** Use a sterile, non-pyrogenic, low protein-binding 0.2 or 0.22 micron in-line filter. • **7-day bags:** Do not use an in-line filter.	• Use an approved infusion pump.[8] • Programmable, lockable, non-elastomeric.[1] • Has an alarm[1] (visual and auditory).[8] • Compatible with IV tubing.[1]	• Ideally infuse through a **multi-lumen central line** (e.g., peripherally inserted central catheter [PICC] or tunneled central venous access device [CVAD]) to ensure continuous infusion and access for additional IV medications and lab draws.[2] • When administering via a multi-lumen venous catheter, infuse blinatumomab through a **dedicated line**.[1]

Infusion Rates by Duration and Dose for Patients Weighing ≥ 45 kg[1]

- Blinatumomab IV bags may be prepared for **continuous infusion over 5 durations**.
- Verify the prescribed dose and infusion duration for each infusion bag.

Storage and Stability Requirements

- Store IV tubing and bag at 2°C to 8°C if not used immediately.
- Do <u>not</u> freeze.
- Prepared infusion bags do <u>not</u> need to be protected from ambient lighting.

Infusion Duration (per IV bag)		Dose[a]	Infusion Rate
Prepared with preservative-free solutions	24 hours (1 day)	9 mcg/day	10 mL/hour
		28 mcg/day	**10 mL/hour**
	48 hours (2 days)	9 mcg/day	5 mL/hour
		28 mcg/day	**5 mL/hour**
	72 hours (3 days)	9 mcg/day	3.3 mL/hour
		28 mcg/day	**3.3 mL/hour**
	96 hours (4 days)	9 mcg/day	2.5 mL/hour
		28 mcg/day	**2.5 mL/hour**
Prepared with bacterio-static saline (containing benzyl alcohol)	7 days	**28 mcg/day**	**0.6 mL/hour**

[a]The 9 mcg/day dose is used during step-up dosing in cycle 1 induction for relapsed or refractory BCP-ALL and dose reductions due to adverse events.

Infusion Interruption and Discontinuation

Setting	Interruption Guidance
Hospital	• Follow institutional protocol for guidance on pausing the infusion.
Home	• The infusion should never be paused (except for port reaccessing).[7]
Acute problems	• If blinatumomab must be stopped for an acute problem, the 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.[7]

Duration of Interruption[1]	Interruption Guidance[1]
≥ 4 hours	• HCP supervision or hospitalization is recommended for re-initiation. • Hospitalization and dexamethasone may be necessary. • Always speak with the physician before re-initiating blinatumomab infusion.
≤ 7 days	• Continue **same cycle** to a **total of 28 days of infusion** (including days before and after dose interruption in that cycle).
> 7 days	• Start a **new cycle**.

Catheter Patency and Occlusion

Follow institutional policies/guidelines for maintaining catheter patency and addressing catheter occlusion.

Maintaining Catheter Patency (Data on File, Amgen 2016)[9]

- Follow institutional policy, provided there is no flushing of blinatumomab.
- Steps:
  1. Disconnect blinatumomab IV bag and tubing.
  2. Withdraw blood through line to clear line of blinatumomab (blood volume not specified[a]).
  3. Flush with saline per institutional practice.

[a]Blood volume may be dependent on type of CVAD used.

Catheter Occlusion (Guidance from University of Maryland Medical Centre)[2]

- **DO NOT FLUSH**; flushing of occluded catheter could cause an adverse event.
- Attempt to aspirate occluded catheter.
  - If aspiration from the catheter fails, **DO NOT FLUSH**.
  - Contact physician for next steps.
  - Document details of situation and personnel involved.
- A fully occluded catheter requires removal and replacement; notify physician with goal of keeping treatment interruption to < 4 hours; notify appropriate clinical teams per institutional protocol (e.g., CVAD team to evaluate line, interventional radiology, PICC nurse[a])

[a]Expert opinion.

Inpatient and Outpatient Transition and Community Care

Once tolerability is established, clinically stable patients may be transitioned to the outpatient setting with frequent follow up with their healthcare team.

Clinic Visits for Outpatients[2,8]

- Minimum weekly clinic visits are advised.
- Ensure a knowledgeable care team member is available at all times.

Hospital Readmission Guidance[1,5]

- Reasons for readmission may include infections, fever, and drug-related toxicity requiring in-patient monitoring and management (e.g., neurotoxicity, ICANS).[5]
- If blinatumomab infusion has been interrupted for **≥ 4 hours**, supervision by a healthcare professional or hospital readmission is recommended.[1]

Safety Profile

Most Common Adverse Events from Clinical Trials (Occurring at ≥ 20%, Any Grade)[1]:

- Infections, (febrile) neutropenia
- Pyrexia, chills
- Anemia, neutropenia, leukopenia, thrombocytopenia, lymphopenia
- Infusion-related reactions
- Headache
- Nausea
- Tremor
- Musculoskeletal pain
- Diarrhea

Common Serious Adverse Events[1]:

- Cytokine release syndrome (CRS)
- Neurologic toxicities including ICANS
- Infections
- Tumour lysis syndrome (TLS)

Recommended Clinical Monitoring

Serious Warnings & Precautions[1]

Clinical Assessment Considering Syndromes and Conditions
Infusion reactions[1]
Infection signs and symptoms[1]
Cytokine release syndrome (CRS)[1] • Headache, pyrexia, hypotension, asthenia, nausea, total bilirubin increased, liver enzymes increased,[1] hypoxia.[10] • Median onset of 2 days.[1]
Disseminated intravascular coagulation (DIC)[1] • 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;[11] increased INR; decreased fibrinogen.[12]
Capillary leak syndrome (CLS)[1] • Edema, hypotension, elevated hematocrit.[13]
Tumour lysis syndrome (TLS)[1] • Monitor for signs and symptoms including renal function and fluid balance.[1,14] • Monitor blood levels of potassium, uric acid, phosphorus, calcium, creatinine.[1] • Closely monitor in first 48 hours and as clinically indicated.[1]
Neurologic events including immune effector cell-associated neurotoxicity syndrome (ICANS)[1] • Headache, tremor, encephalopathy, dizziness, convulsions, difficulty communicating, speech disorders, confusion, disorientation, altered consciousness, disturbances in coordination or balance, reduced pain or touch sensation, paresthesia, seizure activity.[1] • Median time to first event within first 2 weeks.[1]
Speech clarity, cognition/mentation, handwriting[2,8] • Assess once per shift if inpatient[5] and once per clinic visit if outpatient. • If ICANS symptoms are present at any grade, obtain an immune effector cell-associated encephalopathy (ICE) score and repeat every 8 hours or more frequently as indicated.[4]
Pancreatitis[1] • Abdominal pain/tenderness, nausea, vomiting.[1]
Lab Tests
• **CBC**[14] (with differential; including WBC, ANC, hematocrit, INR, fibrinogen).[12] • **Liver function** (ALT, AST, GGT, total bilirubin)[3] and **renal function** (creatinine).[1] • **Calcium, potassium, phosphorus, uric acid**.[1]

Proactive Measures for TLS, Pancreatitis, Neutropenia/Serious Infection

Toxicity	Proactive Measures
TLS	• Consider prophylactic measures, especially if high tumour burden or higher leukocytosis[1]: • Leukoreduction with steroids prior to initiating blinatumomab; IV hydration; antihyperuricemic therapies (e.g., allopurinol or rasburicase). • Monitor closely for TLS signs and symptoms including renal function, electrolytes, uric acid, and fluid balance in the **first 48 hours following the first infusion**.[1,14]
Pancreatitis[1]	• Routinely assess for signs and symptoms
Neutropenia/ serious infection[1]	• Monitor laboratory parameters (including WBC, ANC) during blinatumomab infusion. • Monitor for infection signs and symptoms. • Assess for device-related infection and manage as appropriate.

Dose Modifications for Grade 3 and 4 Adverse Reactions[1]

Grade	Guidance for Patients ≥ 45 kg
Grade 3 (severe) ●●●	• 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) ●●●●	• Consider discontinuing blinatumomab permanently.

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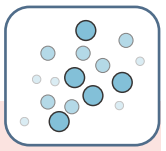
Cytokine Release Syndrome (CRS)



- Suspected CRS should prompt a thorough patient assessment and physician involvement.
- **Mechanism:** T-cell activation causes a surge of cytokine release.[15]
- **Median time to onset:** 2 days (in clinical trials).[1]

Description

- Cytokine release syndrome is a systemic inflammatory reaction.[15]
- CRS most often presents as **flu-like symptoms** including fever, myalgia, arthralgia, headache, and tachycardia.[16]
- **Serious adverse events** that may be associated with CRS include[1,2]:
  - Asthenia
  - Pyrexia
  - Headache
  - Hypotension
  - ↑ liver enzymes (AST, ALT)
  - ↑ total bilirubin
  - Nausea
  - Tachycardia
  - Respiratory distress
  - Hypoxia
- **Severe and fatal CRS** has occurred in patients receiving blinatumomab.[1]
- **CRS has been commonly associated with capillary leak syndrome (CLS) and disseminated intravascular coagulation (DIC)**; uncommonly associated with hemophagocytic histiocytosis/macrophage activation syndrome (MAS).[1]
- **Infusion reactions may be clinically indistinguishable** from CRS manifestations.[3] Infusion reactions include hypotension, hypertension, fever, myalgia, tachypnea, face swelling, and rash.[5]

Proactive Measures

Premedication

- Steroids are recommended prior to blinatumomab infusion.[1]

Parameter/standing orders

- Consider parameter/standing orders for as-needed dexamethasone and tocilizumab per institutional CRS guidelines for prompt treatment of CRS.[2]

Monitoring

- Closely observe for infusion reactions, especially during the first infusion of cycles 1–2.[1]
- Monitor liver enzymes (AST, ALT, GGT) and total bilirubin prior to start of and during treatment.[1]
- Monitor patients for signs and symptoms of CLS and DIC.[1]

Toxicity Management

- This guidance primarily reflects recommendations from the Product Monograph[1] and US Prescribing Information.[6]
- BC Cancer[17] and Cancer Care Ontario provide recommendations on CRS management; however, they are not specific to blinatumomab.
- Blinatumomab's short half-life should be considered in the management strategy.
- HCPs should be aware of institutional protocols for management of CRS.

Management by Grade for Patients ≥ 45 kg[1]

Any grade	• Provide vigilant supportive care.[2,18] • Assess for tumour lysis.[2] • Investigate cause of fever (e.g., blood and urine cultures, chest imaging), provide broad-spectrum antibiotics until infection is ruled out, and assess for febrile neutropenia.[2] • Consider daily monitoring of CRP to identify and monitor CRS.[2a]
Grade 2	• Consider interrupting blinatumomab until ≤ grade 1 (mild).[17,19] • Consider corticosteroid per institutional guidelines.
Grade 3	• Interrupt blinatumomab until ≤ grade 1 (mild).[1] • Treat with dexamethasone 8 mg (PO or IV) every 8 hours for up to 3 days; then taper over 4 days.[6b] • Once resolved, restart blinatumomab at 9 mcg/day; escalate to 28 mcg/day after 7 days if the toxicity does not recur.[1,6]
Grade 4	• Discontinue blinatumomab permanently.[1] • Treat with dexamethasone 8 mg (PO or IV) every 8 hours for up to 3 days; then taper over 4 days.[6b]

[a]Expert opinion.
[b]Recommended in US Prescribing Information, not Health Canada-approved.

Tocilizumab (IL-6 inhibitor)[2]

- If no improvement following drug cessation and steroid treatment, consider tocilizumab per institutional CRS guidelines.
- Avoid tocilizumab in patients with serious CNS toxicities.

Neurotoxicity including Immune Effector Cell-Associated Neurotoxicity (ICANS)

- Nurses play a critical role in early detection of neurotoxicity and ICANS; prompt recognition and escalation is essential and can be life-saving.
- **Mechanism:** Not fully understood[20]; T-cell activation resulting in elevated inflammatory cytokines, disrupting the blood-brain barrier, resulting in neurological dysfunction.[21]
- **Median time to onset:** within first 2 weeks.[1]

Description

- ICANS is a clinically significant neurological complication that has been observed in patients undergoing T-cell-activating immunotherapies.[21]
- Neurologic toxicities including ICANS can be serious or life-threatening.[1]

Leukoencephalopathy[1]:

- Cranial MRI changes indicative of leukoencephalopathy have been observed.

Patients potentially at higher risk:

- Cranial MRI changes observed especially in patients with **prior cranial irradiation and anti-leukemic chemotherapy**.[1]
- **Elderly patients (≥ 65 yo)** experienced a higher rate of neurologic AEs.[1]
- **Prior neurological events** have been associated with a higher risk of neurological toxicity.[20]

Proactive Measures

- **Perform a neurological examination prior to initiating blinatumomab and clinically monitor for neurologic signs and symptoms, including ICANS[1]:**
  - Headache
  - Tremor
  - Encephalopathy
  - Dizziness
  - Convulsions, seizure activity
  - Speech disorders
  - Confusion
  - Disorientation
  - Altered consciousness
  - Disturbances in coordination or balance
- **Assess the following at least once per shift if inpatient,[5] and every clinic visit if outpatient,[a] during therapy:**
  - Speech clarity changes
  - Cognition and/or mentation changes.
- **If ICANS symptoms are present at any grade, obtain an immune effector cell-associated encephalopathy (ICE) score and repeat every 8 hours or more frequently as indicated.[4]**

[a]Expert opinion.

Immune Effector Cell-Associated Encephalopathy (ICE) Score[4,22]

➲ standard tool for assessing and grading ICANS; follow institutional protocol

Category	Points
1. Orientation: orientation to year, month, city, place[a]	4 points
2. Naming: ability to name 3 objects (i.e., pen, cup, glasses)[a]	3 points
3. Following commands: ability to follow simple command (i.e., "Close your eyes and stick out your tongue")	1 point
4. Writing: ability to write a standard sentence (i.e., "The flag is red and white")	1 point
5. Attention: ability to count backwards from 100 by 10	1 point

[a]***1 point for each item. Scoring:*** *7–9 points = ICANS grade 1; 3–6 points = ICANS grade 2; 0–2 points = ICANS grade 3; 0 points = ICANS grade 4*

Toxicity Management for Patients ≥ 45 kg

Event/Grade	Guidance
Seizure	• If > 1 seizure occurs, permanently discontinue blinatumomab.[1] • Consider appropriate secondary prophylaxis or supportive treatment (e.g., anti-epileptics for seizures).[1,20]
Leukoencephalopathy	• If suspected, consider consultation with a neurologist, CSF examination, and brain MRI.[1] • If confirmed, discontinue blinatumomab.[14]
Grade 2 ICANS	• Consider administering corticosteroids and/or performing other actions as clinically indicated (e.g., neurology imaging/consult[a]).[1]
Grade 3 neurologic events including ICANS[1]	• Interrupt until ≤ grade 1 and for ≥ 3 days. • Restart at 9 mcg/day; escalate to 28 mcg/day after 7 days if no recurrence. • Re-initiation: premedicate with dexamethasone (up to 24 mg) with a 4-day taper. • Secondary prophylaxis: consider appropriate anticonvulsant medication. • Discontinue permanently if toxicity occurred at 9 mcg/day, or toxicity takes > 7 days to resolve. • If ICANS, administer corticosteroids and manage according to current practice guidelines.
Grade 4 neurologic events including ICANS[1]	• Discontinue blinatumomab permanently. • If ICANS, administer corticosteroids and manage according to current practice guidelines.

[a]Expert opinion.

Steroids for Severe Symptoms

- Steroids (e.g., dexamethasone) may be used to treat severe symptoms (e.g., encephalopathy, aphasia).[2,20]

Patient and Caregiver Education for CRS and Neurotoxicity/ICANS

CRS, CLS, and DIC

- Educate patients and caregivers to recognize and report signs and symptoms of CRS, CLS, and DIC.
  - **Cytokine release syndrome (CRS):** a systemic inflammatory response.[15]
    - Fever, weakness/tiredness, headache, dizziness, low blood pressure, nausea/vomiting, chills, face swelling, skin rash, trouble breathing/wheezing.[1]
  - **Capillary leak syndrome (CLS):** a manifestation of severe CRS; cytokines cause increased vascular permeability.[13]
    - Trouble breathing, muscle aches, abdominal pain, increased thirst.[13]
  - **Disseminated intravascular coagulation (DIC):** a complication of severe CRS; cytokine storm activates clotting pathways.[23]
    - 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.[11]

Neurotoxicity and ICANS

- Educate patients and caregivers to recognize and report signs and symptoms of neurotoxicity and ICANS (including how to assess ICE scores at home).
  - **Neurological problems:** Difficulty communicating, skin tingling, seizure, tremor/shaking, difficulty remembering, difficulty thinking/processing thoughts, loss of balance.[1,20]
  - **Progressive multifocal leukoencephalopathy (PML):** Progressive weakness and speech, visual or personality changes.[24]
- Advise patients to refrain from driving and engaging in hazardous occupations/activities while blinatumomab is being administered.[1]

Patient and Caregiver Education Checklist

Ensure patients can manage and self-monitor blinatumomab therapy at home with appropriate caregiver/home support.

- ✓ Type of treatment and treatment goal
- ✓ How blinatumomab is administered
- ✓ Care of catheter/infusion site
- ✓ Care of infusion pump (including any troubleshooting guidelines and patient activities that may affect the pump)
- ✓ Signs and symptoms of serious side effects and importance of reporting these to the HCP team
  - Recognizing presentation of ICANS and understanding how to take an ICE score
- ✓ Other medications
- ✓ Fertility, pregnancy, and breastfeeding warnings (for patients of childbearing potential)
- ✓ Available social support services

Scan to access the full clinical resource on CANO's website

Note: Institutional practices relating to blinatumomab therapy may vary across Canada.

Acronyms and Abbreviations

AE, adverse event; ALL, acute lymphoblastic leukemia; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BCP-ALL, B-cell precursor acute lymphoblastic leukemia; BiTE®, bispecific T-cell engager; CBC, complete blood count; CD19, cluster of differentiation 19; CD3, cluster of differentiation 3; CLS, capillary leak syndrome; CNS, central nervous system; CRP, C-reactive protein; CRS, cytokine release syndrome; CSF, cerebral spinal fluid; CVAD, central venous access device; DEHP, di-ethylhexylphthalate; DIC, disseminated intravascular coagulation; EVA, ethyl vinyl acetate; GGT, gamma-glutamyl transferase; HCP, healthcare professional; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; IL-6, interleukin-6; INR, international normalized ratio; IV, intravenous; MAS, macrophage activation syndrome; MRD, minimal or measurable residual disease; MRI, magnetic resonance imaging; PICC, peripherally inserted central catheter; PML, progressive multifocal leukoencephalopathy; PO, by mouth; PVC, polyvinyl chloride; TLS, tumour lysis syndrome; WBC, white blood cell count.

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