Drug Monograph

A - Drug Name

blinatumomab

COMMON TRADE NAME(S): Blincyto®

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B - Mechanism of Action and Pharmacokinetics

Blinatumomab binds the CD3/T-cell receptor complex with CD19 on malignant B-cells, including precursor ALL cells. Activation of the T-cell receptor signaling cascade results in lysis of CD19-expressing cells.

Absorption	With continuous intravenous infusion (CIV), mean steady state serum concentrations were achieved within a day. Pharmacokinetics appeared linear over a dose range of 5 to 90 mcg/m^2/day.	
Distribution	Mainly distributed in the vascular space	
Metabolism	Catabolized to small peptides and amino acids	
Elimination	Half-life	(terminal): 2.1 hours
	Urine	0.2% (60 mcg/m^2/day CIV)

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C - Indications and Status

Health Canada Approvals:

- Acute lymphoblastic leukemia (ALL)

Refer to the product monograph for a full list of approved indications.

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: None

The following adverse effects were reported in the Phase III study in adults with relapsed or refractory B-cell precursor ALL. Severe and life-threatening adverse effects from other clinical trials or post-marketing may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Hypertension (7%)	E
	Hypotension (12%)	E
Dermatological	Rash (14%)	E
General	Edema (17%)	E
	Fever (60%) (7% severe)	E
Hematological	↓ Immunoglobulins (10%)	E
	Myelosuppression ± infection, bleeding (27%) (21% severe)	E
	Other - hematophagic histiocytosis (1%)	E
Hepatobiliary	↑ LFTs (17%) (10% severe)	E
	Pancreatitis (rare; may be severe)	E D
Hypersensitivity	Hypersensitivity (2%)	I
	Infusion related reaction (34%) (3% severe)	I E
Immune	Antibody response (2%)	E
	Cytokine release syndrome (14%) (may be severe)	I E

Metabolic / Endocrine	Tumor lysis syndrome (4%)	E
Musculoskeletal	Musculoskeletal pain (13%)	E
Nervous System	Cranial neuropathy (rare; may be severe)	E
	Dizziness (7%)	E
	Encephalopathy (1%)	E D
	Headache (29%)	E
	Insomnia (10%)	E
	Peripheral neuropathy (5%)	E
	Seizure (2%)	E
	Somnolence (5%)	E
	Tremor (10%)	E
Ophthalmic	Visual disorders (6%) (blurred vision)	E
Respiratory	Cough, dyspnea (15%)	E
Vascular	Capillary leak syndrome (<1%) (maybe severe)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for blinatumomab include fever, infusion related reaction, headache, myelosuppression ± infection, bleeding, ↑ LFTs, edema, cough, dyspnea, rash, musculoskeletal pain and hypotension.

Infusion reactions are common and may not be distinguishable from **cytokine release syndrome** (CRS). Patients should be closely monitored for these, especially during the first infusion of the first 2 cycles. It is important to start at the recommended doses (for Cycle 1, days 1 to 7).

CRS may be severe and sometimes fatal with a median time to onset of 2 days. It may be accompanied by disseminated intravascular coagulation (DIC) and/or capillary leak syndrome (CLS). Premedication with dexamethasone is recommended. **Hematophagocytic histiocytosis/macrophage activation syndrome** (MAS) is uncommonly reported.

Patients at risk of **tumour lysis syndrome** (i.e. high tumour burden) should have appropriate prophylaxis and be monitored closely.

Severe infections, including atypical ones, have been reported and may be fatal. Patients with an ECOG performance status of 2 or higher are at increased risk. Grade 3 or 4 febrile neutropenia was reported in 25% of patients.

Neurologic events were reported in approximately 50% of adult and 25% of pediatric patients. The median time to onset was within the first 2 weeks of starting blinatumomab and was generally reversible. Severe events, which may be fatal, for adult patients included encephalopathy, seizures, speech disorders, cognitive disturbances, co-ordination and balance disorders.

Leukoencephalopathy has been reported rarely, especially in patients who received prior cranial irradiation and chemotherapy (i.e. high dose methotrexate or intrathecal cytarabine).

Life-threatening, sometimes fatal **pancreatitis** has been reported in the clinical trial and post-market setting; in some cases high dose steroids may have been a contributing factor. The diagnosis of pancreatitis should be considered in patients who have severe upper abdominal pain accompanied with nausea, vomiting or abdominal tenderness. If pancreatitis is suspected, blinatumomab should be held or discontinued.

Less than 2% of blinatumomab treated adult patients tested positive for **anti-blinatumomab antibodies**; in the majority of these patients, the antibodies had in-vitro neutralizing activity. Contact the manufacturer to discuss antibody testing if anti-blinatumomab antibodies with a clinically significant effect is suspected.

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E - Dosing

Refer to protocol by which patient is being treated.

Premedication with dexamethasone and CNS prophylaxis with intrathecal chemotherapy (before and during treatment) are recommended.

Patients at risk of tumour lysis syndrome should have appropriate prophylaxis.

MRD-positive B-cell Precursor ALL:

- Hospitalization is recommended at minimum for 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).

Relapsed or Refractory B-cell Precursor ALL:

- Hospitalization is recommended at minimum for the first 9 days of cycle 1 and the first 2 days of cycle 2 to monitor for infusion reactions that are clinically indistinguishable from CRS.
- Dexamethasone up to 24 mg/day for up to 4 days before the first dose of blinatumomab is recommended for patients with ≥ 50% leukemic blasts in the bone marrow or > 15 x 10^9/L peripheral blood leukemic blast count.

Adults:

Pre-medications (prophylaxis for infusion reaction):

MRD-positive	Relapsed or Refractory
• 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	• Dexamethasone 20mg IV given 1 hour before the first dose of each cycle. • An antipyretic is recommended during the first 48 hours of each cycle

Blinatumomab is given as an IV continuous infusion for 28 days, repeated every 6 weeks.

MRD-positive B-cell Precursor ALL:

- Given as **1 induction** cycle followed by 3 consolidation cycles

Patient Weight	Treatment Cycle 1*		Subsequent Cycles*	
	Days 1-28 (as IV continuous infusion)	**Days 29-42**	**Days 1-28** (as IV continuous infusion)	**Days 29-42**
≥ 45kg (fixed-dose)	28 mcg/day	14-day treatment-free interval	28 mcg/day	14-day treatment-free interval
< 45 kg, (BSA-based dose)	15 mcg/m^2/day (maximum 28 mcg/day)		15 mcg/m^2/day (maximum 28 mcg/day)	

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

Relapsed or Refractory B-cell Precursor ALL:

- Given as **2 induction** cycles followed by 3 consolidation cycles.

Induction and Consolidation:

Patient Weight	**Treatment Cycle 1***			**Subsequent Cycles***	
	Days 1-7 (as IV continuous infusion)	**Days 8-28** (as IV continuous infusion)	**Days 29-42**	**Days 1-28** (as IV continuous infusion)	**Days 29-42**
≥ 45kg (fixed-dose)	9 mcg/day	28 mcg/day	14-day treatment-free interval	28 mcg/day	14-day treatment-free interval
< 45 kg, (BSA-based dose)	5 mcg/m^2/day (maximum 9 mcg/day)	15 mcg/m^2/day (maximum 28 mcg/day)		15 mcg/m^2/day (maximum 28 mcg/day)	

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

Refer to the product monograph for information on maintenance treatment (Not funded by NDFP).

Dosage with Toxicity:

Dose should be withheld or discontinued for toxicity as recommended.

T**oxicity**	**Grade**	**Patients ≥ 45kg**	**Patients < 45kg**
Neurotoxicity	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 24mg dexamethasone with a 4-day taper. Consider appropriate	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 at least 0.2-0.4 mg/kg/day dexamethasone (maximum of 24mg) and taper the dose by 25% per day.

		anticonvulsant medication. Discontinue if toxicity occurred at 9 mcg/day, or if toxicity takes more than 7 days to resolve.	Consider appropriate 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.	
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. Weight 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.	See restart
3	• Stop treatment. • Aggressively manage symptoms. **Restart:** After resolution of all symptoms, treatment can be resumed. 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).

Dosage with 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.

Dosage with 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.

Dosage based on gender:

Gender does not appear to influence the pharmacokinetics of blinatumomab.

Children:

Refer to the product monograph for comprehensive pre-medication and dosing information in this population. Blinatumomab has not been administered to patients with a BSA < 0.4m^2.

In general, adverse reactions in pediatric patients treated with blinatumomab were similar in

type to those seen in adult patients. The preservative benzyl alcohol has been associated with potentially fatal toxicity ("gasping syndrome") in neonates. Avoid dosage forms or diluents containing benzyl alcohol in neonates and infants.

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F - Administration Guidelines

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.

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G - Special Precautions

Contraindications:

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

Other 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. Due to the potential for neurological events, including seizures, patients should refrain from driving and engaging in hazardous activities while receiving blinatumomab.
- 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

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Mutagenicity: Unknown
- Embryotoxicity: Unknown
- Teratogenicity: Unknown
  It is not known if blinatumomab can cause fetal harm, but animal studies have demonstrated that the drug crosses the placental barrier. The risk associated with the fetal exposure to the preservative benzyl alcohol through maternal drug administration is unknown. Blinatumomab is not recommended for use in pregnancy and adequate contraception should be used by both

sexes during treatment, and for at least **48 hours** after the last dose.

- Excretion into breast milk: Unknown
  Given the potential for blinatumomab to cause adverse effects in infants, breastfeeding is not recommended while receiving the drug and for at least **48 hours** after the last treatment.
- Fertility effects: Unknown

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H - Interactions

No formal drug interaction studies have been conducted. Blinatumomab causes a transient release of cytokines that may suppress CYP450 enzymes, especially during the first 9 days of the first cycle and the first 2 days of the second cycle. Patients receiving concomitant substrates of CYP450, especially those with a narrow therapeutic index, may be at risk of substrate toxicity.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP 2C9 substrates (e.g. warfarin, meloxicam, fluvastatin)	increased risk of substrate toxicity	blinatumomab treatment may suppress CYP450	monitor and adjust dose of narrow therapeutic range substrates (e.g. warfarin)
CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	increased risk of substrate toxicity	blinatumomab treatment may suppress CYP450	monitor and adjust dose of narrow therapeutic range substrates (e.g. cyclosporine)

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
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 h 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 - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Blinatumomab - Relapsed or Refractory Acute Lymphoblastic Leukemia (Ph+ BCP-ALL)
- Blinatumomab - Relapsed or Refractory Acute Lymphoblastic Leukemia (Ph- BCP-ALL)
- Blinatumomab - Minimal Residual Disease (MRD)-Positive B-cell Precursor Acute Lymphoblastic Leukemia
- Blinatumomab - Relapsed or Refractory Pediatric Acute Lymphoblastic Leukemia

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K - References

Blinatumomab (Blincyto) product monograph. Amgen Canada Inc. May 2021.

Blinatumomab (Blincyto) prescribing information. Amgen Inc. (USA). March 2021.

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.

Kantarjian H, Stein A, Gokbuget N, at al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N Engl J Med. 2017; 376:836-47.

Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol. 2015 Jan;16(1):57-66.

Von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia. Journal of Clinical Oncology. 2016 Dec 20; 34(36):4381-4389.

December 2023 Updated Dosing-Adults and Dosing-Children sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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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.

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