PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrBLINCYTO®

blinatumomab

Lyophilized powder for solution for infusion, 38.5 mcg

Professed Standard

Anti-neoplastic Agent

BLINCYTO, indicated for the treatment of:

- Patients with Philadelphia chromosome-negative CD19 positive B-precursor acute lymphoblastic leukemia (ALL) in first or second hematologic complete remission with minimal residual disease (MRD) greater than or equal to 0.1%
- Pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL,

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for BLINCYTO please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html"

BLINCYTO, indicated for:

- Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

has been issued market authorization without conditions.

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Date of Initial Authorization:
December 22, 2015

Date of Revision:
May 6, 2021

Submission Control Number: 247178

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

1 INDICATIONS	12/2019
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	12/2019
4 DOSAGE AND ADMINISTRATION • 4.2 Recommended Dose and Dosage Adjustment, • 4.3 Reconstitution, • 4.4 Administration • 4.5 Missed Dose	XX/2021
7 WARNING AND PRECAUTIONS	XX/2021

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

BLINCYTO® (blinatumomab) is indicated for the treatment of:

- Patients with Philadelphia chromosome-negative CD19 positive B-precursor acute lymphoblastic leukemia (ALL) in first or second hematologic complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.

  Patients are to be selected for treatment based on detection of minimal residual disease as determined by an accredited laboratory using validated assay methods.
- Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).
- Pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL.

1.1 Pediatrics

Pediatrics (< 18 years of age): The safety of BLINCYTO has been established and effectiveness has been investigated in pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (see **7 WARNINGS AND PRECAUTIONS**, **Special Populations, Pediatrics**).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Compared to younger adults (18 - 64 years of age), elderly patients (≥ 65 years of age) experienced a higher rate of neurologic events including cognitive disorder, encephalopathy, and confusion (see **7 WARNINGS AND PRECAUTIONS, Neurologic and Special Populations**).

2 CONTRAINDICATIONS

BLINCYTO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Cytokine Release Syndrome (CRS), which may be severe, life-threatening or fatal, occurred in patients receiving BLINCYTO (see **7 WARNINGS AND PRECAUTIONS, Immune, Cytokine Release Syndrome**). Clinically significant infusion reactions, which may be indistinguishable from CRS, have been observed (see **7 WARNINGS AND PRECAUTIONS, General, Infusion Reactions**).
- Tumour Lysis Syndrome (TLS), which may be severe, life-threatening or fatal, has been observed in patients receiving BLINCYTO (see **7 WARNINGS AND PRECAUTIONS, Immune, Tumour Lysis Syndrome**).
- Neurological events, including severe, life-threatening, and fatal events, occurred in patients receiving BLINCYTO (see **7 WARNINGS AND PRECAUTIONS, Neurologic; 14 CLINICAL TRIALS**).
- In patients receiving BLINCYTO, serious infections, some of which were life-threatening or fatal, have been observed (see **7 WARNINGS AND PRECAUTIONS, Infections**). The fatal infections included sepsis, pneumonia, Fusarium infection, pneumonia fungal, septic shock, Aspergillus infection, bronchopneumonia, Candida infection, Enterococcal bacteremia, Escherichia sepsis and lung infection.
- Pancreatitis, including severe, life-threatening, and fatal events occurred in patients receiving BLINCYTO in clinical trials and the post-marketing setting (see **7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Pancreatitis**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Hospitalization is recommended for part of the treatment cycle (see **4.2 Recommended Dose and Dosage Adjustment,** Hospitalization)
- Premedication with dexamethasone and intrathecal chemotherapy CNS prophylaxis are recommended (see **4.2 Recommended Dose and Dosage Adjustment,** Premedication and Additional Medication Recommendations)
- Pre-phase treatment is recommended for patients with a high tumour burden (see **4.2 Recommended Dose and Dosage Adjustment,** Pre-phase Treatment for Patients with High Tumour Burden)
- BLINCYTO is compatible with polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags

4.2 Recommended Dose and Dosage Adjustment

Treatment of MRD-positive B-cell Precursor ALL

Hospitalization

Hospitalization is recommended at a minimum for the first 3 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiation (eg, if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended.

Premedication and Additional Medication Recommendations

Intrathecal chemotherapy prophylaxis is recommended before and during BLINCYTO therapy to prevent central nervous system ALL relapse.

- For adult patients, premedicate with prednisone 100 mg intravenously or equivalent (e.g., dexamethasone 16 mg) 1 hour prior to the first dose of BLINCYTO of each cycle.
- For pediatric patients, premedicate with 5 mg/m^2 of dexamethasone, to a maximum dose of 20 mg, within 30 minutes prior to the first dose of BLINCYTO in the first cycle and when restarting an infusion after an interruption of 4 or more hours in the first cycle.

Dosage

BLINCYTO is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump. A single cycle of treatment is 28 days (4 weeks) of continuous infusion followed by a 14-day (2-week) treatment-free interval. Patients may receive 1 cycle of induction treatment followed by 3 additional cycles of BLINCYTO consolidation treatment.

See table below for the recommended dose by patient weight and schedule. Patients greater than or equal to 45 kg receive a fixed-dose. For patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

Table 1. BLINCYTO Recommended Dosage For MRD-positive B-cell Precursor ALL

<table>
<tr><th rowspan="2">Patient Weight</th><th colspan="2">Induction Cycle 1</th><th colspan="2">Consolidation Cycles 2 - 4</th></tr>
<tr><th>Days 1-28</th><th>Days 29-42</th><th>Days 1-28</th><th>Days 29-42</th></tr>
<tr><td>Greater than or equal to 45 kg (fixed-dose)</td><td>28 mcg/day</td><td rowspan="2">14-day treatment-free interval</td><td>28 mcg/day</td><td rowspan="2">14-day treatment-free interval</td></tr>
<tr><td>Less than 45 kg (BSA-based dose)</td><td>15 mcg/m^2/day (not to exceed 28 mcg/day)</td><td>15 mcg/m^2/day (not to exceed 28 mcg/day)</td></tr>
</table>

The safety and efficacy of BLINCYTO in patients weighting less than 45 kg, was established in patients with relapsed or refractory B-cell precursor ALL who received 5 mcg/m^2/day on Days 1-7 of Cycle 1 and 15 mcg/m^2/day for subsequent cycles. The efficacy of BLINCYTO for treatment of MRD-positive ALL in patients weighing less than 45 kg has not been established in clinical trials.

Treatment of Relapsed or Refractory B-cell Precursor ALL

Hospitalization

Hospitalization is recommended at a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and reinitiation (eg, if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended.

Premedication and Additional Medication Recommendations

Intrathecal chemotherapy CNS prophylaxis is recommended before and during BLINCYTO therapy to prevent central nervous system ALL relapse.

Additional premedication recommendations are as follows:

Patient Group	Premedication
Adults (≥ 18 years of age)	Premedicate with dexamethasone 20 mg intravenously 1 hour prior to the first dose of BLINCYTO of each cycle.
Pediatrics (< 18 years of age)	Premedicate with dexamethasone 10 mg/m^2 (not to exceed 20 mg) orally or intravenously 6 to 12 hours prior to the start of BLINCYTO (cycle 1 day 1), followed by premedication with dexamethasone 5 mg/m^2 orally or intravenously within 30 minutes prior to the start of BLINCYTO (cycle 1 day 1).

Pre-phase Treatment for Patients with High Tumour Burden

For pediatric and adult patients with ≥ 50% leukemic blasts in bone marrow or > 15 x 10^9/L peripheral blood leukemic blast counts treatment with dexamethasone (not to exceed 24 mg/day) for up to 4 days prior to the first dose of BLINCYTO is recommended.

Treatment Cycles and Infusion Time

BLINCYTO is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump. A single cycle of treatment is 28 days (4 weeks) of continuous infusion followed by a 14-day (2 week) treatment-free interval. Patients may receive 2 cycles of induction treatment followed by 3 additional cycles of BLINCYTO consolidation treatment.

Maintenance therapy of up to 4 additional cycles may be given following consolidation treatment.

BLINCYTO infusion bags should be admixed to infuse over 24 hours, 48 hours, 72 hours, 96 hours, or 7 days (see **4.3 Reconstitution** and **4.4 Administration**).

Dosage

See table below for the recommended daily dose by patient weight. Patients greater than or equal to 45 kg receive a fixed-dose and for patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

Table 2. BLINCYTO Recommended Dosage for Relapsed or Refractory B-cell Precursor ALL

Cycle	Patient Weight Greater Than or Equal to 45 kg *(Fixed-dose)*	Patient Weight Less Than 45 kg *(BSA-based dose)*
Induction Cycle 1		
Days 1-7	9 mcg/day	5 mcg/m^2/day *(not to exceed 9 mcg/day)*
Days 8-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
Induction Cycle 2		
Days 1-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
Consolidation Cycles 3-5		
Days 1-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
Continued Therapy Cycles 6-9		
Days 1-28	28 mcg/day	15 mcg/m^2/day *(not to exceed 28 mcg/day)*
Days 29-84	56-day treatment-free interval	56-day treatment-free interval

Dose Adjustment

If the interruption after an adverse event is 7 days or less, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse event is longer than 7 days, start a new cycle.

Table 3. Dose Interruptions, Reductions and Discontinuations due to Adverse Events

Toxicity	Grade*	Patients Greater Than or Equal to 45 kg	Patients Less Than 45 kg
Cytokine Release Syndrome (CRS)	Grade 3	Interrupt BLINCYTO until no more than Grade 1 (mild), regardless of the dose at which CRS occurred, restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.	Interrupt BLINCYTO until no more than Grade 1 (mild), regardless of the dose at which CRS occurred, restart BLINCYTO at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur
	Grade 4	Discontinue BLINCYTO permanently.	
Neurologic Events	Seizure	Discontinue BLINCYTO permanently if more than one seizure occurs.	
	Grade 3	Interrupt BLINCYTO until no more than Grade 1 (mild) and for at least 3 days, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. For reinitiation, premedicate with up to 24 mg dexamethasone with a 4-day taper. As secondary prophylaxis, consider appropriate anticonvulsant medication. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently.	Interrupt BLINCYTO until no more than Grade 1 (mild) and for at least 3 days, then restart BLINCYTO at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur. For reinitiation premedicate with at least 0.2-0.4 mg/kg/day dexamethasone (up to a maximum of 24 mg) and taper the dose by 25% per day. Consider appropriate anticonvulsant medication. If the toxicity occurred at 5 mcg/m^2/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently.
	Grade 4	Discontinue BLINCYTO permanently.	
Other Clinically Relevant Adverse Reactions	Grade 3	Interrupt BLINCYTO until no more than Grade 1 (mild), then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue BLINCYTO permanently.	Interrupt BLINCYTO until no more than Grade 1 (mild), then restart BLINCYTO at 5 mcg/m^2/day. Escalate to 15 mcg/m^2/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue BLINCYTO permanently.
	Grade 4	Consider discontinuing BLINCYTO permanently.	

*Based on the Common Terminology Criteria for Adverse Events (CTCAE). Grade 3 is severe, and Grade 4 is life-threatening.

Special Preparation Considerations

It is very important that the instructions for preparation (including admixing) provided in this section are strictly followed to minimize medication errors (including underdose and overdose) (see **7 WARNINGS AND PRECAUTIONS**, **General**, Medication Errors).

Change of IV bag

The intravenous bag must be changed by a healthcare professional for sterility reasons.

BLINCYTO can be infused over 24 hours (preservative-free), 48 hours (preservative-free), 72 hours (preservative-free), 96 hours (preservative-free), or 7 days (with preservative). The choice between 24 hours, 48 hours, 72 hours, 96 hours or 7 days for the infusion duration should be made by the treating physician considering the frequency of the infusion bag changes and the weight of the patient. The administration of BLINCYTO as a 7-day infusion is not recommended for patients weighing less than 22 kg.

For preparation, reconstitution, and administration of BLINCYTO:

- See **4.3 Reconstitution** and **4.4 Administration** for infusion over 24 hours, 48 hours, 72 hours, or 96 hours using 0.9% Sodium Chloride
- See **4.3 Reconstitution** and **4.4 Administration** for infusion over 7 days using Bacteriostatic 0.9% Sodium Chloride (containing 0.9% benzyl alcohol). This option is available for patients weighing greater than or equal to 22 kg. It is not recommended for use in patients weighing less than 22 kg.

Aseptic Preparation

Strictly observe aseptic technique when preparing the solution for infusion since BLINCYTO vials do not contain antimicrobial preservatives. To prevent accidental contamination, prepare BLINCYTO according to aseptic standards, including but not limited to:

- Preparation must be done in a clean, aseptic environment
- Preparation must be done in an ISO Class 5 laminar flow hood or better
- The admixing area should have appropriate environmental specifications, confirmed by periodic monitoring
- Personnel should be appropriately trained in aseptic manipulations and admixing of oncology drugs
- Personnel should wear appropriate protective clothing and gloves
- Gloves and surfaces should be disinfected

Package Content

1 package of BLINCYTO includes 1 vial of BLINCYTO and 1 vial of IV Solution Stabilizer.

- **Do not use IV Solution Stabilizer for reconstitution of BLINCYTO**. IV Solution Stabilizer is provided with the BLINCYTO package and is used to coat the intravenous bag prior to addition of reconstituted BLINCYTO to prevent adhesion of BLINCYTO to intravenous bags and intravenous tubing.
- More than 1 package of BLINCYTO may be needed to prepare the recommended dose.

Incompatibility Information

BLINCYTO is incompatible with di-ethylhexylphthalate (DEHP) due to the possibility of particle formation, leading to a cloudy solution.

- Use polyolefin, PVC DEHP-free, or ethyl vinyl acetate (EVA) infusion bags
- Use polyolefin, PVC DEHP-free, or EVA intravenous tubing sets

4.3 Reconstitution

Preparation of BLINCYTO as 24-Hour-, 48-Hour, 72-Hour or 96-Hour Infusion

Reconstitute BLINCYTO with preservative-free Sterile Water for Injection. Do not reconstitute BLINCYTO vials with the IV Solution Stabilizer.

To prime the intravenous tubing, use only the solution in the bag containing the FINAL prepared BLINCYTO solution for infusion. Do not prime with 0.9% Sodium Chloride.

Reconstitution of BLINCYTO for 24-Hour, 48-Hour, 72-Hour or 96-Hour Infusion

1. Determine the number of BLINCYTO vials needed for a dose and infusion duration.
2. Reconstitute each BLINCYTO vial with **3 mL of preservative-free Sterile Water for Injection** by directing the water along the walls of the BLINCYTO vial and not directly on the lyophilized powder. The resulting concentration per BLINCYTO vial is 12.5 mcg/mL.
   - Do not reconstitute BLINCYTO vials with IV Solution Stabilizer.
3. **Gently swirl contents to avoid excess foaming.**
   - Do not shake.
4. **Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion.** The resulting solution should be clear to slightly opalescent, colourless to slightly yellow.
   - Do not use if solution is cloudy or has precipitated.

Preparation of BLINCYTO Infusion Bag for 24-Hour, 48-Hour, 72-Hour, or 96-Hour Infusion

Verify the prescribed dose and infusion duration for each BLINCYTO infusion bag. To minimize errors, **use the specific volumes described in Tables 4 and 5 to prepare the BLINCYTO infusion bag.**

- Table 4 for patients weighing greater than or equal to 45 kg
- Table 5 for patients weighing less than 45 kg

1. **Aseptically add 270 mL 0.9% Sodium Chloride to the empty intravenous bag**. If a pre-filled intravenous bag is used, ensure that the intravenous bag volume is 270 mL including any intravenous bag overfill. BLINCYTO dose calculations provided in Tables 4 and 5 are based on a starting volume of 270 mL 0.9% Sodium Chloride.
2. **Aseptically transfer 5.5 mL IV Solution Stabilizer to the intravenous bag containing 0.9% Sodium Chloride.** Gently mix the contents of the bag to avoid foaming. Discard the vial containing the unused IV Solution Stabilizer.

3. **Aseptically transfer the required volume of reconstituted BLINCYTO solution** into the intravenous bag containing 0.9% Sodium Chloride and IV Solution Stabilizer. Gently mix the contents of the bag to avoid foaming.
   - Refer to Table 4 for patients weighing greater than or equal to 45 kg for the specific volume of reconstituted BLINCYTO.
   - Refer to Table 5 for patients weighing less than 45 kg (dose based on BSA) for the specific volume of reconstituted BLINCYTO.
   - Discard the vial containing unused BLINCYTO.
4. Under aseptic conditions, attach the intravenous tubing to the intravenous bag with the sterile 0.2 or 0.22 micron in-line filter. Ensure that the intravenous tubing is compatible with the infusion pump.
5. Remove air from the intravenous bag. This is particularly important for use with an ambulatory infusion pump.
6. **Prime the intravenous tubing only with the solution in the bag containing the FINAL prepared BLINCYTO solution for infusion.**
7. Store refrigerated at 2°C to 8°C if not used immediately (see **11 STORAGE, STABILITY AND DISPOSAL**).

Table 4. For Patients Weighing Greater Than or Equal to 45 kg: Volumes to add to Intravenous Bag

0.9% Sodium Chloride (starting volume)			270 mL	
IV Solution Stabilizer (fixed volume for 24, 48, 72, and 96-hour infusion durations)			5.5 mL	
Infusion Duration	**Dose**	**Infusion Rate**	**Reconstituted BLINCYTO**	
			Volume	**Vials**
24 hours	9 mcg/day	10 mL/hour	0.83 mL	1
	28 mcg/day	10 mL/hour	2.6 mL	1
48 hours	9 mcg/day	5 mL/hour	1.7 mL	1
	28 mcg/day	5 mL/hour	5.2 mL	2
72 hours	9 mcg/day	3.3 mL/hour	2.5 mL	1
	28 mcg/day	3.3 mL/hour	8 mL	3
96 hours	9 mcg/day	2.5 mL/hour	3.3 mL	2
	28 mcg/day	2.5 mL/hour	10.7 mL	4

Table 5. For Patients Weighing Less Than 45 kg: Volumes to add to Intravenous Bag

0.9% Sodium Chloride (starting volume)				270 mL	
IV Solution Stabilizer (fixed volume for 24, 48, 72, and 96-hour infusion durations)				5.5 mL	
Infusion Duration	**Dose**	**Infusion Rate**	**BSA (m^2)**	**Reconstituted BLINCYTO**	
				Volume	**Vials**
24 hours	5 mcg/m^2/day	10 mL/hour	1.5 – 1.59	0.7 mL	1
			1.4 – 1.49	0.66 mL	1
			1.3 – 1.39	0.61 mL	1
			1.2 – 1.29	0.56 mL	1
			1.1 – 1.19	0.52 mL	1
			1 – 1.09	0.47 mL	1
			0.9 – 0.99	0.43 mL	1
			0.8 – 0.89	0.38 mL	1
			0.7 – 0.79	0.33 mL	1
			0.6 – 0.69	0.29 mL	1
			0.5 – 0.59	0.24 mL	1
			0.4 – 0.49	0.2 mL	1
24 hours	15 mcg/m^2/day	10 mL/hour	1.5 – 1.59	2.1 mL	1
			1.4 – 1.49	2 mL	1
			1.3 – 1.39	1.8 mL	1
			1.2 – 1.29	1.7 mL	1
			1.1 – 1.19	1.6 mL	1
			1 – 1.09	1.4 mL	1
			0.9 – 0.99	1.3 mL	1
			0.8 – 0.89	1.1 mL	1
			0.7 – 0.79	1 mL	1
			0.6 – 0.69	0.86 mL	1
			0.5 – 0.59	0.72 mL	1
			0.4 – 0.49	0.59 mL	1

Table 5. For Patients Weighing Less Than 45 kg: Volumes to add to Intravenous Bag

0.9% Sodium Chloride (starting volume)				270 mL	
IV Solution Stabilizer (fixed volume for 24, 48, 72, and 96-hour infusion durations)				5.5 mL	
Infusion Duration	**Dose**	**Infusion Rate**	**BSA (m^2)**	**Reconstituted BLINCYTO**	
				Volume	**Vials**
48 hours	5 mcg/m^2/day	5 mL/hour	1.5 – 1.59	1.4 mL	1
			1.4 – 1.49	1.3 mL	1
			1.3 – 1.39	1.2 mL	1
			1.2 – 1.29	1.1 mL	1
			1.1 – 1.19	1 mL	1
			1 – 1.09	0.94 mL	1
			0.9 – 0.99	0.85 mL	1
			0.8 – 0.89	0.76 mL	1
			0.7 – 0.79	0.67 mL	1
			0.6 – 0.69	0.57 mL	1
			0.5 – 0.59	0.48 mL	1
			0.4 – 0.49	0.39 mL	1
48 hours	15 mcg/m^2/day	5 mL/hour	1.5 – 1.59	4.2 mL	2
			1.4 – 1.49	3.9 mL	2
			1.3 – 1.39	3.7 mL	2
			1.2 – 1.29	3.4 mL	2
			1.1 – 1.19	3.1 mL	2
			1 – 1.09	2.8 mL	1
			0.9 – 0.99	2.6 mL	1
			0.8 – 0.89	2.3 mL	1
			0.7 – 0.79	2 mL	1
			0.6 – 0.69	1.7 mL	1
			0.5 – 0.59	1.4 mL	1
			0.4 – 0.49	1.2 mL	1

Table 5. For Patients Weighing Less Than 45 kg: Volumes to add to Intravenous Bag

0.9% Sodium Chloride (starting volume)				270 mL	
IV Solution Stabilizer (fixed volume for 24, 48, 72, and 96-hour infusion durations)				5.5 mL	
Infusion Duration	**Dose**	**Infusion Rate**	**BSA (m^2)**	**Reconstituted BLINCYTO**	
				Volume	**Vials**
72 hours	5 mcg/m^2/day	3.3 mL/hour	1.5 – 1.59	2.1 mL	1
			1.4 – 1.49	2 mL	1
			1.3 – 1.39	1.8 mL	1
			1.2 – 1.29	1.7 mL	1
			1.1 – 1.19	1.6 mL	1
			1 – 1.09	1.4 mL	1
			0.9 – 0.99	1.3 mL	1
			0.8 – 0.89	1.1 mL	1
			0.7 – 0.79	1 mL	1
			0.6 – 0.69	0.86 mL	1
			0.5 – 0.59	0.72 mL	1
			0.4 – 0.49	0.59 mL	1
72 hours	15 mcg/m^2/day	3.3 mL/hour	1.5 – 1.59	6.3 mL	3
			1.4 – 1.49	5.9 mL	3
			1.3 – 1.39	5.5 mL	2
			1.2 – 1.29	5.1 mL	2
			1.1 – 1.19	4.7 mL	2
			1 – 1.09	4.2 mL	2
			0.9 – 0.99	3.8 mL	2
			0.8 – 0.89	3.4 mL	2
			0.7 – 0.79	3 mL	2
			0.6 – 0.69	2.6 mL	1
			0.5 – 0.59	2.2 mL	1
			0.4 – 0.49	1.8 mL	1

Table 5. For Patients Weighing Less Than 45 kg: Volumes to add to Intravenous Bag

0.9% Sodium Chloride (starting volume)				270 mL	
IV Solution Stabilizer (fixed volume for 24, 48, 72, and 96-hour infusion durations)				5.5 mL	
Infusion Duration	**Dose**	**Infusion Rate**	**BSA (m^2)**	**Reconstituted BLINCYTO**	
				Volume	**Vials**
96 hours	5 mcg/m^2/day	2.5 mL/hour	1.5 – 1.59	2.8 mL	1
			1.4 – 1.49	2.6 mL	1
			1.3 – 1.39	2.4 mL	1
			1.2 – 1.29	2.3 mL	1
			1.1 – 1.19	2.1 mL	1
			1 – 1.09	1.9 mL	1
			0.9 – 0.99	1.7 mL	1
			0.8 – 0.89	1.5 mL	1
			0.7 – 0.79	1.3 mL	1
			0.6 – 0.69	1.2 mL	1
			0.5 – 0.59	0.97 mL	1
			0.4 – 0.49	0.78 mL	1
96 hours	15 mcg/m^2/day	2.5 mL/hour	1.5 – 1.59	8.4 mL	3
			1.4 – 1.49	7.9 mL	3
			1.3 – 1.39	7.3 mL	3
			1.2 – 1.29	6.8 mL	3
			1.1 – 1.19	6.2 mL	3
			1 – 1.09	5.7 mL	3
			0.9 – 0.99	5.1 mL	2
			0.8 – 0.89	4.6 mL	2
			0.7 – 0.79	4 mL	2
			0.6 – 0.69	3.4 mL	2
			0.5 – 0.59	2.9 mL	2
			0.4 – 0.49	2.3 mL	1

Preparation of BLINCYTO as 7 Day Infusion using Bacteriostatic 0.9% Sodium Chloride (Preservative)

Use preservative-free Sterile Water for Injection to reconstitute BLINCYTO. Do not reconstitute BLINCYTO vials with the IV Solution Stabilizer.

Do not use an inline filter with a 7-day infusion bag.

Prime the intravenous tubing only with the solution in the bag containing the FINAL prepared solution for infusion. Do not prime with 0.9% Sodium Chloride.

Reconstitution of BLINCYTO for 7-Day Infusion

1. Determine the number of BLINCYTO vials needed for a dose.
2. Reconstitute each BLINCYTO vial with **3 mL of preservative-free Sterile Water for Injection** by directing the water along the walls of the BLINCYTO vial and not directly on the lyophilized powder. The resulting concentration per BLINCYTO vial is 12.5 mcg/mL.
   - Do not reconstitute BLINCYTO vials with the IV Solution Stabilizer.
3. **Gently swirl contents to avoid excess foaming.**
   - Do not shake.
4. **Visually inspect the reconstituted solution for particulate matter and discolouration during reconstitution and prior to infusion.** The resulting solution should be clear to slightly opalescent, colourless to slightly yellow.
   - Do not use if solution is cloudy or has precipitated.

Preparation of BLINCYTO Infusion Bag for 7-Day Infusion

Verify the prescribed dose and infusion duration for each BLINCYTO infusion bag. To minimize errors, **use the specific volumes described in Table 6 to prepare the BLINCYTO infusion bag**.

1. **Aseptically add 90 mL Bacteriostatic 0.9% Sodium Chloride to the empty intravenous bag.**
2. **Aseptically transfer 2.2 mL IV Solution Stabilizer to the intravenous bag containing the Bacteriostatic 0.9% Sodium Chloride.** Gently mix the contents of the bag to avoid foaming. Discard the vial containing the unused IV Solution Stabilizer.
3. **Aseptically transfer the required volume of reconstituted BLINCYTO solution** into the IV bag containing the saline solution and IV Solution Stabilizer. Gently mix the contents of the bag to avoid foaming.
   - Refer to Table 6 for the specific volume of reconstituted BLINCYTO. Discard the vial containing unused BLINCYTO.
4. **Aseptically add the required volume of 0.9% Sodium Chloride to the intravenous bag to obtain a final volume of 110 mL.** Gently mix the contents of the bag to avoid foaming.
   - Refer to Table 6 for the specific volume of 0.9% Sodium Chloride.
5. Under aseptic conditions, attach the intravenous tubing to the intravenous bag.
   - Ensure that the intravenous tubing is compatible with the infusion pump.

- **Do not use an inline filter for a 7-day bag.**

6. Remove air from the intravenous bag. This is particularly important for use with an ambulatory infusion pump.
7. **Prime the intravenous tubing only with the solution in the bag containing the FINAL prepared BLINCYTO solution for infusion.**
8. Store refrigerated at 2°C to 8°C if not used immediately (see **11 STORAGE, STABILITY AND DISPOSAL**).

Table 6. For 7-Day Infusion: Volumes to add to Intravenous Bag for 28 mcg/day and 15 mcg/m²/day

Bacteriostatic 0.9% Sodium Chloride (starting volume)				90 mL	
IV Solution Stabilizer (fixed volume for 7-day infusion)				2.2 mL	
Reconstituted BLINCYTO				Specific volume listed below in table	
Quantity Sufficient (qs) with 0.9% Sodium Chloride to a Final Volume of 110 mL				Specific volume listed below in table	
Infusion Duration				7 days	
Infusion Rate				0.6 mL/hour	
Patient Weight	**Dose**	**BSA (m^2)**	**Reconstituted BLINCYTO**		**Volume of 0.9% Sodium Chloride needed to q.s. to a Final Volume of 110 mL**
			Volume	**Vials**	
Fixed-Dose					
Greater than or equal to 45 kg	28 mcg/day	N/A	16.8 mL	6	1 mL
BSA-Based Dose					
22 kg to less than 45 kg	15 mcg/m^2/day	1.5 – 1.59	14 mL	5	3.8 mL
		1.4 – 1.49	13.1 mL	5	4.7 mL
		1.30 – 1.39	12.2 mL	5	5.6 mL
		1.20 – 1.29	11.3 mL	5	6.5 mL
		1.10 – 1.19	10.4 mL	4	7.4 mL
		1 – 1.09	9.5 mL	4	8.3 mL
		0.9 – 0.99	8.6 mL	4	9.2 mL
Less than 22 kg	**7-day infusion not recommended**				

4.4 Administration

Administration of BLINCYTO for 24-Hour, 48-Hour, 72-Hour, or 96-Hour Infusion

- Administer BLINCYTO as a continuous intravenous infusion at a constant flow rate using an infusion pump. The pump should be programmable, lockable, non-elastomeric, and have an alarm.
- The starting volume (270 mL) is more than the volume administered to the patient (240 mL) to account for the priming of the intravenous tubing and to ensure that the patient will receive the full dose of BLINCYTO.
- Infuse prepared BLINCYTO final infusion solution according to the instructions on the pharmacy label on the prepared bag at one of the following constant infusion rates:
  - Infusion rate of 10 mL/hour for a duration of 24 hours, OR
  - Infusion rate of 5 mL/hour for a duration of 48 hours, OR
  - Infusion rate of 3.3 mL/hour for a duration of 72 hours, OR
  - Infusion rate of 2.5 mL/hour for a duration of 96 hours
- Administer prepared BLINCYTO final infusion solution using intravenous tubing that contains a sterile, non-pyrogenic, low protein-binding, 0.2 or 0.22 micron in-line filter. For a 7-day bag administration information, see **Administration of BLINCYTO as a 7-Day Infusion Bag** below.
- **Important Note: Do not flush the BLINCYTO infusion line or intravenous catheter, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage and complications thereof. When administering via a multi lumen venous catheter, infuse BLINCYTO through a dedicated lumen.**
- At the end of the infusion, discard any unused BLINCYTO solution in the intravenous bag and intravenous tubing in accordance with local requirements.

Administration of BLINCYTO as a 7-Day Infusion Bag

Administration of BLINCYTO as a 7-day infusion is not recommended for patients weighing less than 22 kg (see **7 WARNINGS AND PRECAUTIONS, General,** Benzyl Alcohol Toxicity and **Pediatrics**, Benzyl Alcohol Toxicity and Pediatrics).

- Administer BLINCYTO as a continuous intravenous infusion at a constant flow rate using an infusion pump. The pump should be programmable, lockable, non-elastomeric, and have an alarm.
- The final volume of infusion solution (110 mL) will be more than the volume administered to the patient (100 mL) to account for the priming of the intravenous tubing and to ensure that the patient will receive the full dose of BLINCYTO.
- **Do not use an inline filter for a 7-day bag.**
- Infuse prepared BLINCYTO final infusion solution according to the instructions on the pharmacy label on the prepared bag at an infusion rate of 0.6 mL/hour for a duration of 7 days.

- **Important Note: Do not flush the BLINCYTO infusion line or intravenous catheter, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage and complications thereof. When administering via a multi lumen venous catheter, infuse BLINCYTO through a dedicated lumen.**
- At the end of the infusion, dispose of any unused BLINCYTO solution in the intravenous bag and intravenous tubing in accordance with local requirements.

4.5 Missed Dose

If the interruption due to a missed dose is 7 days or less, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the missed dose in that cycle. If an interruption due to a missed dose is longer than 7 days, start a new cycle.

5 OVERDOSAGE

Overdoses have been observed including one patient who received 133-fold the recommended therapeutic dose of BLINCYTO delivered over a short duration. Overdoses resulted in adverse reactions that were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, the infusion should be temporarily interrupted and patients should be monitored. Consider reinitiation of BLINCYTO at the correct therapeutic dose (see **4 DOSAGE AND ADMINISTRATION**).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognize the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 7. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Lyophilized powder for solution for infusion / 38.5 mcg	Citric acid monohydrate, lysine hydrochloride, polysorbate 80, sodium hydroxide and trehalose dihydrate

Each BLINCYTO package contains:

- BLINCYTO supplied in a single-use vial as a sterile, preservative-free, white to off-white lyophilized powder containing 38.5 mcg of blinatumomab per vial. The following non-medicinal ingredients are contained in the vial: citric acid monohydrate, trehalose dihydrate, lysine hydrochloride, Polysorbate 80 and sodium hydroxide.
- IV Solution Stabilizer supplied in a 10 mL single-use glass vial as a sterile, preservative-free, colourless-to-slightly yellow, clear solution. Do not use the IV Solution Stabilizer to reconstitute BLINCYTO. The following non-medicinal ingredients are contained in the vial: citric acid monohydrate, lysine hydrochloride, Polysorbate 80, sodium hydroxide and water for injection

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

General

Infusion Reactions

Infusion reactions may be clinically indistinguishable from manifestations of cytokine release syndrome (CRS) (see **7 WARNINGS AND PRECAUTIONS, Immune**, Cytokine Release Syndrome). Premedication with dexamethasone is recommended (see **4.2 Recommended Dose and Dosage Adjustment**).

Patients should be observed closely for infusion reactions, especially during the first infusion of the first and second cycles, and treated appropriately. Management of infusion reactions may require either temporary interruption or discontinuation of BLINCYTO (see **4 DOSAGE AND ADMINISTRATION**).

Medication Errors

Medication errors have occurred with BLINCYTO treatment. It is very important that the instructions for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose) (see **4 DOSAGE AND ADMINISTRATION** and **5 OVERDOSAGE**).

Patients less than 45 kg must be administered BLINCYTO based on body surface area calculations (mcg/m^2/day) and not at the fixed mcg/day dosing regimen (see **4 DOSAGE AND ADMINISTRATION**).

Benzyl Alcohol Toxicity

Serious and fatal adverse reaction including “gasping syndrome” can occur in pediatric patients, particularly in neonates and infants treated with BLINCYO containing the benzyl alcohol preservative. The “gasping syndrome” is characterized by central nervous syndrome depression, metabolic acidosis, and gasping respirations.

When prescribing BLINCYTO with benzyl alcohol preservative to patients, consider the combined daily metabolic load of benzyl alcohol from all sources of drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth weight infants may be more likely to develop adverse reactions (see **7.1 Special Populations, Pregnant Women** and **7.1 Special Populations, Pediatrics**).

Due to the addition of bacteriostatic saline, 7-day bags of BLINCYTO solution for infusion contain benzyl alcohol and are not recommended for use in patients weighing less than 22 kg (see **4 DOSAGE AND ADMINISTRATION**, **Administration, Administration of BLINCYTO as a 7- Day Infusion Bag**; **7.1 Special Populations, Pregnant Women** and **7.1 Special Populations, Pediatrics**).

CD19-Negative Relapse

Relapse of CD19-negative B-precursor ALL has been reported in patients receiving BLINCYTO in clinical trials and the post-marketing setting. BLINCYTO is not recommended in patients with CD19-negative disease including those who have relapsed with CD19-negative disease after prior anti-CD19 therapy. Particular attention should be given to assessment of CD19 expression at the time of bone marrow testing.

Lineage Switch from ALL to Acute Myeloid Leukemia (AML)

Lineage switch from ALL to AML has been reported in patients receiving BLINCYTO in clinical trials and the post-marketing setting. Patients who had documented immunophenotypic and/or cytogenetic abnormalities at initial diagnosis of B-precursor ALL should be closely monitored for presence of AML since they are predisposed to a lineage switch to AML.

Hepatic/Biliary/Pancreatic

General

Treatment with BLINCYTO was associated with transient elevations in liver enzymes. The majority of these events were observed within the first week of BLINCYTO initiation and did not require BLINCYTO interruption or discontinuation. Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during BLINCYTO treatment, especially when administering BLINCYTO to patients who are receiving other drugs known to be associated with elevations in liver enzymes. Interrupt BLINCYTO if the transaminases rise to greater than 5 times the upper limit of normal or if bilirubin rises to more than 3 times the upper limit of normal (see **4.2 Recommended Dose and Dosage Adjustment**).

Pancreatitis

Pancreatitis, life threatening or fatal, has been reported in patients receiving BLINCYTO in clinical trials and the post-marketing setting. High-dose steroid therapy may have contributed, in some cases, to the pancreatitis.

Evaluate patients who develop signs and symptoms of pancreatitis. The diagnosis of pancreatitis should be considered in patients taking BLINCYTO who experience severe upper abdominal pain accompanied with nausea, vomiting or abdominal tenderness. If pancreatitis is suspected, BLINCYTO should be either temporarily interrupted or discontinued (see **4.2 Recommended Dose and Dosage Adjustment**).

Immune

Cytokine Release Syndrome

Cytokine Release Syndrome (CRS), which may be severe, life-threatening or fatal, was reported in patients receiving BLINCYTO. Serious adverse events that may be associated with CRS included pyrexia, asthenia, headache, hypotension, total bilirubin increased, elevation of liver enzymes (AST and ALT) and nausea.

The median time to onset was 2 days. Patients should be closely monitored for signs or symptoms of these events.

Premedication with dexamethasone is recommended. The dose and duration of premedication is based on age and tumour burden (see **4.2 Recommended Dose and Dosage Adjustment**).

Disseminated intravascular coagulation (DIC) and Capillary leak syndrome (CLS) have been commonly associated with CRS. Life-threatening cases of CLS have been reported in patients receiving BLINCYTO. Patients should be closely monitored for signs or symptoms of these events.

Hemophagocytic histiocytosis/macrophage activation syndrome (MAS) has been uncommonly reported in the setting of CRS.

To mitigate the risk of CRS, it is important to initiate BLINCYTO (cycle 1, days 1-7) at the recommended starting doses in Table 1. Management of CRS events may require either temporary interruption or discontinuation of BLINCYTO (see **4.2 Recommended Dose and Dosage Adjustment**).

Tumour Lysis Syndrome

Tumour lysis syndrome (TLS), which may be severe, life-threatening or fatal, has been observed in patients receiving BLINCYTO. Appropriate prophylactic measures including aggressive hydration and antihyperuricemic therapies (such as allopurinol or rasburicase) should be used for the prevention of TLS during BLINCYTO treatment, especially in patients with higher leukocytosis or a high tumour burden. Patients should be closely monitored for signs or symptoms of TLS, including renal function and fluid balance in the first 48 hours after the first infusion. In clinical studies, patients with moderate renal impairment (30 ≤ CrCL < 60 mL/min) showed an increased incidence of TLS compared with patients with mild renal impairment (60 ≤ CrCL < 90 mL/min) or normal (≥ 90 mL/min) renal function.

Management of these events may require either temporary interruption or discontinuation of BLINCYTO (see **4.2 Recommended Dose and Dosage Adjustment**).

Infections

General

Patients with ALL are immunocompromised and consequently have increased risks for serious infections. In patients receiving BLINCYTO, serious infections, including sepsis, pneumonia, bacteremia, opportunistic infections, and catheter site infections have been observed, some of which were life-threatening or fatal. Fatal infections included sepsis, pneumonia, Fusarium infection, pneumonia fungal, septic shock, *Aspergillus* infection, bronchopneumonia, *Candida* infection, *Enterococcal* bacteremia, *Escherichia* sepsis and lung infection. There is limited experience with BLINCYTO in patients with active uncontrolled infections.

Monitor patients for signs and symptoms of infections and treat appropriately. Management of infections may require either temporary interruption or discontinuation of BLINCYTO (see **4.2 Recommended Dose and Dosage Adjustment**).

BLINCYTO should be prepared by personnel appropriately trained in aseptic manipulations and admixing of oncology drugs. Aseptic technique must be strictly observed when preparing the solution for infusion and when performing routine catheter care (see **4 DOSAGE AND ADMINISTRATION**).

Neutropenia and Febrile Neutropenia

Neutropenia and febrile neutropenia, including life threatening cases, have been observed in patients receiving BLINCYTO. Monitor laboratory parameters (including, but not limited, to white blood cell count and absolute neutrophil count) during BLINCYTO infusion and treat appropriately.

Neurologic

General

Neurologic events (any grade) were observed in approximately 50% of adult patients and in approximately 25% of pediatric patients receiving BLINCYTO. Among patients that experienced a neurologic event, the median time to the first event was within the first two weeks of BLINCYTO treatment and the majority of events resolved. Infrequently, a neurologic event led to treatment discontinuation. Grade 3 or higher (severe, life-threatening and fatal) neurologic events that occurred following the initiation of BLINCYTO for adult patients included: encephalopathy, seizures, speech disorders, disturbances in consciousness, confusion and disorientation, coordination and balance disorders and for pediatric patients included: somnolence, confusional state and neuralgia (see **8.1 Adverse Reaction Overview**).

There is limited experience with BLINCYTO in patients with active ALL in the central nervous system (CNS) or a history of neurologic events. Patients with a history or presence of clinically relevant CNS pathology were excluded from clinical trials.

It is recommended that a neurological examination be performed in patients prior to starting BLINCYTO therapy. Patients receiving BLINCYTO should be clinically monitored for signs and symptoms of neurologic events. Management of these signs and symptoms may require either temporary interruption or discontinuation of BLINCYTO (see **4.2 Recommended Dose and Dosage Adjustment**).

Leukoencephalopathy

Cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving BLINCYTO, especially in patients with prior treatment with cranial irradiation and anti-leukemic chemotherapy (including systemic high dose methotrexate or intrathecal cytarabine). The clinical significance of these imaging changes is unknown.

Due to the potential for progressive multifocal leukoencephalopathy (PML), patients should be monitored for signs and symptoms. In case of suspicious events consider consultation with a neurologist, brain MRI and examination of cerebral spinal fluid (CSF).

Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including seizures, patients receiving BLINCYTO are at risk for loss of consciousness (see **7 WARNINGS AND PRECAUTIONS, Neurologic**).

Advise patients to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO is being administered.

7.1 Special Populations

7.1.1 Pregnant Women

The safety and efficacy of BLINCYTO in pregnant women has not been established. A developmental toxicity study conducted in mice demonstrated that a murine surrogate molecule crossed the placental barrier, indicating the potential for lymphocytopenia. Infants born to mothers exposed to blinatumomab could be at increased risk for infection. There was no indication of maternal toxicity, embryotoxicity, or teratogenicity. The expected depletions of B and T-cells were observed in the pregnant mice but hematological effects were not assessed in fetuses.

Animal studies are not always predictive of human response. Therefore, it is not known whether BLINCYTO can cause fetal harm when administered to a pregnant woman and BLINCYTO should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Women of childbearing potential should use contraception during and for at least 48 hours after treatment with BLINCYTO.

Due to the potential for depletion of B lymphocytes in infants following exposure to BLINCYTO during pregnancy, the infant's B lymphocytes should be monitored before the initiation of live virus vaccination. Live virus vaccines can be administered when the B lymphocytes are within the normal range.

Benzyl Alcohol Toxicity

Due to the addition of bacteriostatic saline, 7-day bags of BLINCYTO solution for infusion contain benzyl alcohol (see **4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Special Preparation Considerations**). The risk associated with fetal exposure to the preservative benzyl alcohol through maternal drug administration is unknown; however, the benzyl alcohol has been shown to cause serious and fatal adverse reactions when administered intravenously to neonates and infants (see **7 WARNINGS AND PRECAUTIONS**, **General**, Benzyl Alcohol Toxicity and **7.1 Special Populations, Pediatrics**).

7.1.2 Breast-feeding

It is not known if BLINCYTO is present in human milk. Because of the potential for BLINCYTO to cause adverse effects in infants, nursing should be discontinued during and for at least 48 hours after treatment with BLINCYTO.

7.1.3 Pediatrics

Pediatrics (< 18 years of age):

The safety of BLINCYTO has been established and effectiveness has been investigated in pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL. In a single-arm phase I/II study (Study MT103-205) of 93 pediatric patients, 70 patients (7 months to 17 years of age) received the recommended mcg/m^2/day dose of BLINCYTO (see **4 DOSAGE AND ADMINISTRATION** and **14 CLINICAL TRIALS)**. In general, adverse reactions in pediatric patients treated with BLINCYTO were similar in type to those seen in adult patients (see **8.1 Adverse Reaction Overview**).

In the dose evaluation phase of the study, one patient experienced a fatal cardiac failure event in the setting of life-threatening cytokine release syndrome (CRS) and tumour lysis syndrome (TLS) and 1 patient experienced a life-threatening capillary leak syndrome resulting in discontinuation of BLINCYTO. Both patients were treated at a 30 mcg/m^2/day (higher than the maximum tolerated/recommended) dose (see **7 WARNINGS AND PRECAUTIONS, Immune**, Cytokine Release Syndrome and Tumour Lysis Syndrome).

Benzyl Alcohol Toxicity and Pediatrics

Due to the addition of bacteriostatic saline, 7-day bags of BLINCYTO solution for infusion containing benzyl alcohol are not recommended for use in any patients weighing less than 22 kg. Prepare BLINCYTO solution for infusion with preservative-free saline (24 hour, 48 hour, 72 hour, or 96 hour bags) for use in neonates, infants, and patients weighing less than 22 kg (see **4 DOSAGE AND ADMINISTRATION)**.

The preservative benzyl alcohol has been associated with serious and fatal adverse reactions in pediatric patients, particularly in premature neonates and infants. The "gasping syndrome" (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages of more than 99 mg/kg/day. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Premature and low-birth weight infants may be more likely to develop these adverse reactions because they may be less able to metabolize benzyl alcohol.

Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources. The minimum amount of benzyl alcohol at which toxicity may occur is not known.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age):

Of the total number of patients in the adult relapsed/refractory ALL studies, approximately 13% were 65 years of age and over. Compared to younger adult (18 - 64 years of age) patients, elderly patients experienced a higher rate of serious neurologic events. The most common serious neurological adverse events that were increased in elderly patients compared to younger adult patients were encephalopathy (13.3%), confusional state (10.0%) and cognitive disorder (6.7%). Serious infections also occurred more frequently among elderly patients (see **7 WARNINGS AND PRECAUTIONS, Neurologic**).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Acute Lymphoblastic Leukemia in Adult Patients (see **14.1 Trial Design and Study demographics**)

The safety data described below reflect exposure to BLINCYTO in a randomized, open-label, active-controlled clinical study (00103311, TOWER Study) in which 376 patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL were treated with BLINCYTO (n = 267) or standard of care (SOC) chemotherapy (n = 109). The median age of BLINCYTO-treated patients in this study was 37 years (range: 18 to 80 years).

The most common treatment-emergent adverse events (≥ 20%) were pyrexia, headache, anemia, febrile neutropenia and diarrhea.

The most common serious treatment-emergent adverse events (≥ 2%) included febrile neutropenia, pyrexia, sepsis, pneumonia, overdose, septic shock, cytokine release syndrome, bacterial sepsis and device-related infection.

Treatment-emergent adverse events leading to treatment discontinuation were reported in 12.4% of subjects receiving blinatumomab. With the exception of histiocytosis hematophagic that occurred in 2 subjects, all other events leading to discontinuation occurred in 1 subject each.

Treatment-emergent adverse events of Grade 3 or higher were reported in 86.5% of patients. Fatal treatment-emergent adverse events occurred in 19.1% of patients. The majority of these events were infections.

In a separate single-arm, phase 2 study of adults with Philadelphia chromosome-positive relapsed or refractory disease (Study 20120216), 45 patients with at least one infusion of blinatumomab were evaluated for safety. The safety profile regarding adverse event reporting was similar to the Philadelphia chromosome-negative patients in the TOWER study. Of the 28 patients with serious treatment-emergent adverse event, the most common events (> 5%) were febrile neutropenia, device-related infection, sepsis, and tremor. Grade 3 or higher treatment-emergent adverse events occurred in 82.2% while 5 cases (11.1%) of fatal adverse events occurred as 1 event each of multi-organ failure, respiratory failure, sepsis, septic shock, and cerebral hemorrhage. These data support a safety profile in these Philadelphia chromosome-positive patients that is qualitatively similar to that reported in the much larger population of Philadelphia chromosome-negative patients in the TOWER study.

In the adult MRD-positive ALL population, treatment-related treatment-emergent adverse events were reported for 97.1% of subject, which is higher than that for R/R ALL population (85.3%). Serious treatment-related treatment-emergent adverse events were also higher in the adult MRD-positive ALL population (50.4%) than R/R ALL population (30.6%). Grade ≥ 3 treatment-related treatment-emergent adverse events were similar between the 2 populations (53.3% vs. 54.2%), 2 cases (1.5%) of fatal adverse events occurred as 1 event each of atypical pneumonia and subdural hemorrhage. There was a higher incidence of treatment-related treatment-emergent adverse events leading to discontinuation of study drug in the adult MRD-positive ALL population (11.7%) as compared to R/R ALL population (7.9%).

Serious neurological treatment-emergent adverse events with a higher incidence rate in the adult MRD-positive ALL population as compared to the R/R ALL population were tremor (5.8% vs. 1.7%), encephalopathy (4.4% vs. 2.0%), aphasia (4.4% vs. 1.3%), seizure (2.9%, vs. 1.4%), ataxia (1.5% vs. 0.4%), and paresthesia (0.7% vs. 0.4%)

The most frequently reported serious treatment-related treatment-emergent adverse events (≥ 2%) in the adult MRD-positive ALL population as compared to the R/R adult ALL were pyrexia (12.4% vs. 3.5%), tremor (5.8% vs. 1.7%), encephalopathy (4.4% vs 2.0%), aphasia (4.4% vs. 1.3%), and lymphopenia (4.4% vs. 0.1%).

Acute Lymphoblastic Leukemia in Pediatric Patients (see **14.1 Trial Design and Study demographics**)

In general, the adverse reactions in the BLINCYTO-treated pediatric patients were similar in type to those seen in adult patients.

The safety data described in this section reflect exposure to BLINCYTO in a clinical trial in which 70 pediatric patients with relapsed or refractory ALL received up to 15 mcg/m^2/day (Study MT103-205). All patients received at least one dose of BLINCYTO. The median age of the study population was 8 years (range: 7 months to 17 years) (see **14 CLINICAL TRIALS**).

The most common adverse reactions (≥ 20%) were pyrexia (80%), anemia (41.4%), nausea (32.9%), headache (30.0%), hypertension (25.7%), vomiting (24.3%), thrombocytopenia (21.4%), hypokalemia (21.4%), febrile neutropenia (20.0%), cough (20.0%) and back pain (20.0%).

Adverse reactions that were observed more frequently in the pediatric population compared to the adult population were rhinitis (10%), hypophosphatemia (14.3%), hypocalcemia (11.4%), hypertension (25.7%), epistaxis (14.3%), and blood lactate dehydrogenase increased (10%).

Adverse reactions of Grade 3 or higher were reported in 87.1% of patients. Discontinuation of therapy due to adverse reactions (CRS, recurrent leukemia, or fungal infection) occurred in 4 out of 70 patients (5.7%) treated with BLINCYTO. Fatal adverse events occurred in 8 out of 70 patients (11.4%), the majority of these events were in the setting of disease progression.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Acute Lymphoblastic Leukemia in Adult Patients

The adverse reactions described in Table 8 reflect experience from the Phase 3, Randomized, Open-Label Study Investigating the Efficacy of the BiTE® Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (TOWER Study).

In the phase 2 study involving more heavily pretreated subjects, the most common serious treatment-emergent adverse events (≥ 2%) included febrile neutropenia, pyrexia, sepsis, pneumonia, device-related infection, neutropenia, confusional state tremor, encephalopathy, overdose, headache, staphylococcal bacteremia and other infections. Encephalopathy was reported in 10 patients (5.3%). Other neurologic events (any grade) suggestive of encephalopathy in more than 5% of patients in the pivotal study included tremor (17.5%), muscular weakness (7.9%) and confusional state (7.4%). The treatment-emergent adverse events reported most frequently as the reason for discontinuation of treatment included sepsis and encephalopathy (see **14 CLINICAL TRIALS)**.

Table 8. Treatment-Emergent Adverse Events in the Phase 3, randomized, open-label clinical trial (N = 376)

Adverse Reaction		BLINCYTO (N = 267)		Standard of Care (SOC) Chemotherapy (N = 109)	
	CIOMS Frequency**	Any Grades* n (%)	≥ Grade 3* n (%)	Any Grades* n (%)	≥ Grade 3* n (%)
Blood and lymphatic system disorders					
Anemia[1, 20]	Very Common	73 (27)	56 (21)	46 (42)	38 (35)
Febrile neutropenia[20]	Very Common	64 (24)	57 (21)	43 (39)	38 (35)
Thrombocytopenia[2, 20]	Very Common	64 (24)	50 (19)	45 (41)	43 (39)
Neutropenia[3, 20]	Very Common	62 (23)	56 (21)	42 (39)	38 (35)
Leukopenia[4, 20]	Common	23 (9)	19 (7)	10 (9)	10 (9)
Leukocytosis[5, 19]	Common	14 (5)	6 (2)	1 (1)	1 (1)
Lymphadenopathy[19]	Common	6 (2)	1 (< 1)	0 (0)	0 (0)
Lymphopenia[6, 20]	Common	5 (2)	4 (1)	4 (4)	4 (4)
Hematophagic histiocytosis[19]	Common	4 (1)	4 (1)	0 (0)	0 (0)

Table 8. Treatment-Emergent Adverse Events in the Phase 3, randomized, open-label clinical trial (N = 376)

Adverse Reaction	CIOMS Frequency**	BLINCYTO (N = 267)		Standard of Care (SOC) Chemotherapy (N = 109)	
		Any Grades* n (%)	≥ Grade 3* n (%)	Any Grades* n (%)	≥ Grade 3* n (%)
Cardiac disorders					
Tachycardia[7, 20]	Very Common	35 (13)	3 (1)	16 (15)	1 (1)
General disorders and administration site conditions					
Pyrexia[8, 19]	Very Common	161 (60)	19 (7)	49 (45)	5 (5)
Edema[9, 20]	Very Common	46 (17)	3 (1)	19 (17)	1 (1)
Chills[20]	Common	19 (7)	1 (< 1)	12 (11)	3 (3)
Chest pain[10, 20]	Common	18 (7)	0 (0)	10 (9)	2 (2)
Pain[19]	Common	16 (6)	6 (2)	6 (6)	0 (0)
Hepatobiliary disorders					
Hyperbilirubinemia[11, 20]	Common	20 (7)	10 (4)	11 (10)	4 (4)
Immune system disorders					
Cytokine release syndrome[19]	Very Common	38 (14)	9 (3)	0 (0)	0 (0)
Hypersensitivity[20]	Common	5 (2)	0 (0)	1 (1)	0 (0)
Cytokine storm[20]	Uncommon	1 (< 1)	0 (0)	0 (0)	0 (0)
Infections and infestations					
Infections - pathogen unspecified[20]	Very Common	116 (43)	63 (24)	56 (51)	38 (35)
Bacterial infectious disorders[20]	Very Common	56 (21)	28 (10)	36 (33)	22 (20)
Viral infectious disorders[19]	Very Common	43 (16)	7 (3)	17 (16)	1 (1)
Fungal infectious disorders[20]	Very Common	34 (13)	16 (6)	18 (17)	11 (10)
Injury, poisoning and procedural complications					
Infusion-related reactions[12, 19]	Very Common	91 (34)	9 (3)	9 (8)	1 (1)
Overdose[19]	Common	8 (3)	0 (0)	0 (0)	0 (0)
Accidental overdose[19]	Common	3 (1)	3 (1)	0 (0)	0 (0)
Investigations					
Hepatic enzyme increased[13, 19]	Very Common	45 (17)	26 (10)	16 (15)	12 (11)
Decreased immunoglobulins[14, 19]	Common	26 (10)	7 (3)	2 (2)	0 (0)
Weight increased[20]	Common	8 (3)	1 (< 1)	4 (4)	0 (0)
Blood alkaline phosphatase increased[19]	Common	7 (3)	3 (1)	4 (4)	0 (0)

Table 8. Treatment-Emergent Adverse Events in the Phase 3, randomized, open-label clinical trial (N = 376)

Adverse Reaction	CIOMS Frequency**	BLINCYTO (N = 267)		Standard of Care (SOC) Chemotherapy (N = 109)	
		Any Grades* n (%)	≥ Grade 3* n (%)	Any Grades* n (%)	≥ Grade 3* n (%)
Metabolism and nutrition disorders					
Tumour lysis syndrome[19]	Common	10 (4)	8 (3)	1 (1)	1 (1)
Musculoskeletal and connective tissue disorders					
Back pain[19]	Very Common	35 (13)	4 (1)	10 (9)	2 (2)
Bone pain[19]	Very Common	30 (11)	6 (2)	8 (7)	0 (0)
Pain in extremity[19]	Common	25 (9)	3 (1)	8 (7)	0 (0)
Nervous system disorders					
Headache[20]	Very Common	77 (29)	1 (< 1)	32 (29)	3 (3)
Tremor[19]	Common	26 (10)	1 (< 1)	0 (0)	0 (0)
Dizziness[20]	Common	18 (7)	1 (< 1)	8 (7)	0 (0)
Somnolence[19]	Common	14 (5)	3 (1)	1 (1)	0 (0)
Paresthesia[19]	Common	13 (5)	0 (0)	1 (1)	0 (0)
Hypoesthesia[19]	Common	7 (3)	0 (0)	0 (0)	0 (0)
Memory impairment[20]	Common	5 (2)	0 (0)	0 (0)	0 (0)
Seizure[20]	Common	5 (2)	2 (1)	4 (4)	3 (3)
Aphasia[20]	Common	4 (1)	1 (< 1)	0 (0)	0 (0)
Cognitive disorder[20]	Common	4 (1)	2 (1)	0 (0)	0 (0)
Encephalopathy[19]	Common	4 (1)	4 (1)	0 (0)	0 (0)
Speech disorder[20]	Uncommon	1 (< 1)	0 (0)	0 (0)	0 (0)
Psychiatric disorders					
Insomnia[20]	Very Common	28 (10)	1 (< 1)	10 (9)	0 (0)
Confusional state[19]	Common	9 (3)	3 (1)	3 (3)	0 (0)
Disorientation[20]	Common	4 (1)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders					
Cough[19]	Very Common	39 (15)	0 (0)	6 (6)	0 (0)
Dyspnea[15, 20]	Common	24 (9)	8 (3)	13 (12)	3 (3)
Productive cough[19]	Common	11 (4)	1 (< 1)	1 (1)	0 (0)
Skin and subcutaneous tissue disorders					
Rash[16, 20]	Very Common	38 (14)	2 (1)	22 (20)	0 (0)

Table 8. Treatment-Emergent Adverse Events in the Phase 3, randomized, open-label clinical trial (N = 376)

Adverse Reaction		BLINCYTO (N = 267)		Standard of Care (SOC) Chemotherapy (N = 109)	
	CIOMS Frequency**	Any Grades* n (%)	≥ Grade 3* n (%)	Any Grades* n (%)	≥ Grade 3* n (%)
Vascular disorders					
Hypotension[17, 20]	Very Common	33 (12)	3 (1)	13 (12)	3 (3)
Hypertension[18, 20]	Common	18 (7)	5 (2)	9 (8)	2 (2)
Flushing[20]	Common	6 (2)	0 (0)	1 (1)	0 (0)

* Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

** the CIOMS Frequency reflects the frequency in the blinatumomab arm

1 Anemia includes anemia and hemoglobin decreased
2 Thrombocytopenia includes platelet count decreased and thrombocytopenia
3 Neutropenia includes neutropenia and neutrophil count decreased
4 Leukopenia includes leukopenia and white blood cell count decreased
5 Leukocytosis includes leukocytosis and white blood cell count increased
6 Lymphopenia includes lymphocyte count decreased and lymphopenia
7 Tachycardia includes sinus tachycardia, supraventricular tachycardia, and tachycardia
8 Pyrexia includes body temperature increased and pyrexia
9 Edema includes face edema, generalized edema, edema, and edema peripheral
10 Chest pain includes chest discomfort, chest pain, musculoskeletal chest pain, and non-cardiac chest pain
11 Hyperbilirubinemia includes blood bilirubin increased and hyperbilirubinemia
12 Infusion-related reactions is a composite term that includes the term infusion-related reaction and the following events occurring with the first 48 hours of infusion and the event lasted ≤ 2 days: pyrexia, cytokine release syndrome, hypotension, myalgia, acute kidney injury, hypertension, and rash erythematous
13 Hepatic enzyme increased includes alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, and transaminases increased
14 Decreased immunoglobulins includes blood immunoglobulin G decreased, globulins decreased, hypogammaglobulinaemia, hypoglobulinaemia, and immunoglobulins decreased
15 Dyspnea includes acute respiratory failure, dyspnea, dyspnea exertional, respiratory failure, and wheezing
16 Rash includes erythema, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, and rash pruritic
17 Hypotension includes blood pressure decreased and hypotension
18 Hypertension includes blood pressure increased and hypertension
19 Events occurring at higher incidence (≥ 2% difference for any grade or ≥ 1% difference for Grade ≥ 3) in blinatumomab-treated patients compared with SOC-chemotherapy treated patients
20 Events that did not meet the threshold defined above but are included as adverse reactions due to biological plausibility

The adverse reaction profile in BLINCYTO-treated patients in this study was similar in type to the supporting Phase 2 study of 225 patients Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia. Thirty-six of these patients were added from the original cohort and followed more intensively for neurological adverse events. No new safety signals were picked up in this study, including the more carefully followed cohort of 36 patients and the toxicity profile of these studies were similar to those seen in the Phase 1/2 single-arm studies in the BLINCYTO development program. Capillary Leak Syndrome was observed in 1 patient in the Open-label, Multicenter, Phase 2 Study to Evaluate Efficacy and Safety of the Bi-specific T cell Engager (BiTE®) Antibody Blinatumomab in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (Study MT103-211).

A total of 45 Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL patients were studied in a Phase 2 single-arm trial (Study 20120216). The adverse reaction profile of 45 patients in a Phase 2 single-arm trial receiving BLINCYTO for Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL patients (Study 20120216) was similar in type to those seen in the Phase 3, randomized, open-label trial (TOWER Study). In particular, neurological events were similar in type and frequency of events, though there were fewer reported cases of encephalopathy (1 case, 2.2%). Aphasia, confusional state, encephalopathy, and tremor led to interruption of treatment in 1 subject each while no patients discontinued therapy due to a neurological event.

MRD-positive B-cell Precursor ALL in Adult Patients

The safety of BLINCYTO in patients with MRD-positive B-cell precursor ALL was evaluated in two single-arm clinical studies in which 137 patients were treated with BLINCYTO. The median age of the study population was 45 years (range: 18 to 77 years).

The most common adverse reactions (≥ 20%) were pyrexia, infusion related reactions, headache, infections (pathogen unspecified), tremor, and chills. Serious adverse reactions were reported in 61% of patients. The most common serious adverse reactions (≥ 2%) included pyrexia, tremor, encephalopathy, aphasia, lymphopenia, neutropenia, overdose, device related infection, seizure, and staphylococcal infection. Adverse reactions of Grade 3 or higher were reported in 64% of patients. Discontinuation of therapy due to adverse reactions occurred in 17% of patients; neurologic events were the most frequently reported reasons for discontinuation. There were 2 fatal adverse events that occurred within 30 days of the end of BLINCYTO treatment (atypical pneumonia and subdural hemorrhage).

Overall the incidence rates of treatment-emergent adverse events were similar between the adult MRD-positive ALL population and the R/R ALL population (99.2% vs 100%). The following treatment-emergent adverse events were reported at higher rate (≥ 5%) in the adult MRD-positive ALL population than the R/R ALL population: pyrexia (90.5% vs. 64.6%), headache (39.4% vs. 31.6%), tremor (29.2% vs. 12.5%), chills (28.5% vs. 10.1%), fatigue (26.3% vs. 14.6%), vomiting (21.2% vs. 15.0%), insomnia (16.1% vs. 9.6%), blood immunoglobulin G decreased (13.9% vs. 2.8%), arthralgia (12.4% vs. 7.4%), aphasia (11.7% vs. 3.0%), C-reactive protein increased (12.4% vs. 4.5%), and blood immunoglobulin A decreased (10.2% vs. 1.4%).

Overall, the incidence rate of neurologic Grade ≥ 3 adverse events was similar between the adult MRD-positive ALL population and the R/R ALL population (16.1% vs. 12.7%). The following neurologic treatment-emergent adverse events had a higher incidence rate (≥ 5%) in the adult MRD-positive ALL population than the R/R ALL population: headache (39.4% vs. 31.6%), tremor (29.2% vs. 12.5%), insomnia (16.1% vs. 9.6%), and aphasia (11.7% vs. 3%).

Table 9 below summarizes the adverse reactions occurring at a ≥ 10% incidence for any grade or ≥ 5% incidence for Grade 3 or higher.

Table 9. Adverse Reactions Occurring at ≥ 10% Incidence for Any Grade or ≥ 5% Incidence for Grade 3 or Higher in BLINCYTO-Treated Patients with MRD-Positive B-cell Precursor ALL (N=137)

Adverse Reaction	Any Grade* n (%)	≥ Grade 3* n (%)
Blood and lymphatic system disorders		
Neutropenia[1]	21 (15)	21 (15)
Leukopenia[2]	19 (14)	13 (9)
Thrombocytopenia[3]	14 (10)	8 (6)
Cardiac disorders		
Arrhythmia[4]	17 (12)	3 (2)
General disorders and administration site conditions		
Pyrexia[5]	125 (91)	9 (7)
Chills	39 (28)	0 (0)
Infections and infestations		
Infections - pathogen unspecified	53 (39)	11 (8)
Injury, poisoning and procedural complications		
Infusion related reaction[6]	105 (77)	7 (5)
Investigations		
Decreased immunoglobulins[7]	25 (18)	7 (5)
Weight increased	14 (10)	1 (<1)
Hypertransaminasemia[8]	13 (9)	9 (7)
Musculoskeletal and connective tissue disorders		
Back pain	16 (12)	1 (<1)
Nervous system disorders		
Headache	54 (39)	5 (4)
Tremor[9]	43 (31)	6 (4)
Aphasia	16 (12)	1 (<1)
Dizziness	14 (10)	1 (<1)
Encephalopathy[10]	14 (10)	6 (4)
Psychiatric disorders		
Insomnia[11]	24 (18)	1 (<1)
Respiratory, thoracic and mediastinal disorders		
Cough	18 (13)	0 (0)

Table 9. Adverse Reactions Occurring at ≥ 10% Incidence for Any Grade or ≥ 5% Incidence for Grade 3 or Higher in BLINCYTO-Treated Patients with MRD-Positive B-cell Precursor ALL (N=137)

Adverse Reaction	Any Grade* n (%)	≥ Grade 3* n (%)
Skin and subcutaneous tissue disorders		
Rash[12]	22 (16)	1 (<1)
Vascular disorders		
Hypotension	19 (14)	1 (<1)

* Grading based on NCI Common Terminology for Adverse Events (CTCAE) version 4.0.

1 Neutropenia includes febrile neutropenia, neutropenia, and neutrophil count decreased.
2 Leukopenia includes leukopenia and white blood cell count decreased.
3 Thrombocytopenia includes platelet count decreased and thrombocytopenia.
4 Arrhythmia includes bradycardia, sinus arrhythmia, sinus bradycardia, sinus tachycardia, tachycardia and ventricular extrasystoles.
5 Pyrexia includes body temperature increased and pyrexia.
6 Infusion-related reaction is a composite term that includes the term infusion-related reaction and the following events occurring with the first 48 hours of infusion and the event lasted ≤ 2 days: cytokine release syndrome, eye swelling, hypertension, hypotension, myalgia, periorbital edema, pruritus generalized, pyrexia, and rash.
7 Decreased immunoglobulins includes blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, hypogammaglobulinemia, hypoglobulinemia, and immunoglobulins decreased.
8 Hypertransaminasemia includes alanine aminotransferase increased, aspartate aminotransferase increased, and hepatic enzyme increased.
9 Tremor includes essential tremor, intention tremor, and tremor.
10 Encephalopathy includes cognitive disorder, depressed level of consciousness, disturbance in attention, encephalopathy, lethargy, leukoencephalopathy, memory impairment, somnolence, and toxic encephalopathy.
11 Insomnia includes initial insomnia, insomnia, and terminal insomnia.
12 Rash includes dermatitis contact, eczema, erythema, rash, and rash maculopapular.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Acute Lymphoblastic Leukemia in Pediatric Patients

BLINCYTO was evaluated in an open-label, multicenter, single-arm phase I/II study of 93 pediatric patients with relapsed or refractory B-cell ALL, in which 70 patients received the recommended 5/15 mcg/m^2/day dose (Study MT103-205). All patients received at least one dose of BLINCYTO. The median age of the study population was 8 years (range: 7 months to 17 years) (see **14 CLINICAL TRIALS**).

Table 10. Treatment-Emergent Adverse Events for Pediatric Patients in Study MT103-205 with ≥ 5% Incidence for Any Grade or Grade 3 or Higher (N = 70) (Safety Analysis Set - 5/15 mcg/m²/day Treatment Cohort)

	MT103-205 5/15 mcg/m²/d	
System Organ Class **Preferred Term**	**Any Grade (%)**	**Grade ≥ 3 (%)**
Blood and lymphatic system disorders	62.9	54.3
Anemia	41.4	35.7
Thrombocytopenia	21.4	21.4
Febrile neutropenia	20.0	17.1
Neutropenia	17.1	17.1
Leukopenia	12.9	10.0
Cardiac disorders	15.7	1.4
Sinus tachycardia	7.1	0.0
Gastrointestinal disorders	64.3	8.6
Nausea	32.9	0.0
Vomiting	24.3	1.4
Abdominal pain	18.6	2.9
Diarrhea	12.9	1.4
Constipation	8.6	0.0
Stomatitis	7.1	0.0
General disorders and administration site conditions	91.4	18.6
Pyrexia	80.0	14.3
Pain	8.6	1.4
Fatigue	7.1	0.0
Edema peripheral	7.1	0.0
Non-cardiac chest pain	5.7	0.0
Immune system disorders	15.7	8.6
Cytokine release syndrome	11.4	5.7
Infections and infestations	50.0	25.7
Infections - pathogen unspecified[1]	38.6	20.0
Viral infectious disorders[1]	10.0	2.9
Bacterial infectious disorders[1]	8.6	4.3
Fungal infectious disorders[1]	5.7	4.3
Investigations	61.4	34.3
Alanine aminotransferase increased	18.6	15.7
Weight increased	17.1	4.3
Aspartate aminotransferase increased	14.3	11.4
Platelet count decreased	14.3	14.3
Neutrophil count decreased	12.9	12.9
White blood cell count decreased	11.4	10.0
Blood lactate dehydrogenase increased	10.0	1.4
Fibrin D dimer increased	8.6	0.0

Table 10. Treatment-Emergent Adverse Events for Pediatric Patients in Study MT103-205 with ≥ 5% Incidence for Any Grade or Grade 3 or Higher (N = 70) (Safety Analysis Set - 5/15 mcg/m²/day Treatment Cohort)

	MT103-205 5/15 mcg/m²/d	
System Organ Class **Preferred Term**	**Any Grade (%)**	**Grade ≥ 3 (%)**
Activated partial thromboplastin time prolonged	5.7	1.4
Blood bilirubin increased	5.7	4.3
Weight decreased	5.7	0.0
Metabolism and nutrition disorders	41.4	21.4
Hypokalemia	21.4	17.1
Hypophosphatemia	14.3	4.3
Hypocalcemia	11.4	4.3
Hyperglycemia	8.6	2.9
Hypomagnesemia	8.6	0.0
Hyponatremia	7.1	1.4
Hypoalbuminemia	5.7	0.0
Musculoskeletal and connective tissue disorders	42.9	5.7
Back pain	20.0	2.9
Pain in extremity	11.4	2.9
Bone pain	10.0	0.0
Arthralgia	5.7	0.0
Muscular weakness	5.7	0.0
Nervous system disorders	48.6	8.6
Headache	30.0	2.9
Tremor	5.7	0.0
Psychiatric disorders	14.3	1.4
Anxiety	5.7	0.0
Respiratory, thoracic and mediastinal disorders	41.4	12.9
Cough	20.0	1.4
Epistaxis	14.3	2.9
Atelectasis	5.7	1.4
Hypoxia	5.7	2.9
Vascular disorders	35.7	5.7
Hypertension	25.7	5.7
Hypotension	14.3	1.4

Adverse events coded using MedDRA version 17.1.
Severity graded using CTCAE v4.0.
Preferred terms with an Incidence >=5% in "Any Grade" or "Grade>=3" columns are displayed in this table.
[1] MedDRA High Level Group Terms (HLGT).

8.3 Less Common Clinical Trial Adverse Reactions

MRD-positive B-cell Precursor ALL in Adult Patients

Additional adverse reactions in patients with MRD-positive ALL that did not meet the threshold criteria for inclusion in Table 9 were:

Blood and lymphatic system disorders: anemia

General disorders and administration site conditions: edema peripheral, pain, and chest pain (includes chest pain and musculoskeletal chest pain)

Hepatobiliary disorders: blood bilirubin increased

Immune system disorders: hypersensitivity and cytokine release syndrome

Infections and infestations: viral infectious disorders, bacterial infectious disorders, and fungal infectious disorders

Injury, poisoning and procedural complications: medication error and overdose (includes overdose and accidental overdose)

Investigations: blood alkaline phosphatase increased

Musculoskeletal and connective tissue disorders: pain in extremity and bone pain

Nervous system disorders: seizure (includes seizure and generalized tonic-clonic seizure), speech disorder, and hypoesthesia

Psychiatric disorders: confusional state, disorientation, and depression

Respiratory, thoracic and mediastinal disorders: dyspnea and productive cough

Vascular disorders: hypertension (includes blood pressure increased and hypertension) flushing (includes flushing and hot flush), and capillary leak syndrome

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Less Common Clinical Trial Adverse Drug Reactions in Pediatrics (< 5%)

Additional important treatment-related adverse events that did not meet the threshold criteria for inclusion in Table 10 were:

Blood and lymphatic system disorders: leukocytosis (2.9%), histiocytosis hematophagic (1.4%), lymphopenia (1.4%)

Cardiac disorders: tachycardia (4.3%)

General disorders and administration site conditions: chills (4.3%), edema (4.3%), asthenia (2.9%), chest pain (2.9%)

Immune system disorders: drug hypersensitivity (2.9%)

Injury, poisoning and procedural complications: overdose (4.3%), infusion related reaction (1.4%)

Investigations: lymphocyte count decreased (4.3%), blood immunoglobulin G decreased (1.4%), blood immunoglobulin M decreased (1.4%), immunoglobulin decreased (1.4%)

***Metabolism and nutrition disorders*:** hyperuricemia (2.9%)

Nervous system disorders: dizziness (4.3%), somnolence (4.3%), convulsion (2.9%), paresthesia (2.9%), peripheral motor neuropathy (2.9%), encephalopathy (1.4%), hypoesthesia (1.4%)

Psychiatric disorders: agitation (4.3%), insomnia (4.3%), irritability (2.9%), confusional state (1.4%), restlessness (1.4%)

Respiratory, thoracic and mediastinal disorders: tachypnea (4.3%), dyspnea (2.9%), productive cough (1.4%)

Skin and subcutaneous disorders: rash maculo-papular (4.3%), rash (1.4%)

Vascular disorders: flushing (4.3%), capillary leak syndrome (2.9%)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Acute Lymphoblastic Leukemia in Adult Patients

Laboratory parameters that had grade 3 or 4 shifts from normal baseline values are presented in the table below.

Table 11. Hematology and Serum Chemistry: Number of adult patients experiencing 3 or 4 Grade shifts from baseline after treatment with BLINCYTO (TOWER Study)

		TOWER Study (N = 267)	
Laboratory Category Laboratory Parameter	**NCI CTCAE Reference Range Version 4.03 (June 2010)**	**Number of subjects with a value change of 3 grade level from baseline, n (%)**	**Number of subjects with a value change of 4 grade level from baseline, n (%)**
Hematology			
Decreased absolute lymphocytes	Grade 3: 0.2 to < 0.5 x 10^9/L Grade 4: < 0.2 x 10^9/L	43 (16.1)	55 (20.6)
Decreased absolute neutrophil granulocytes	Grade 3: 0.5 to < 1.0 x 10^9/L Grade 4: < 0.5 x 10^9/L	24 (9.0)	56 (21.0)
Decreased hemoglobin	Grade 3: 65 to < 80 g/L Grade 4: < 65 g/L	2 (0.7)	0 (0.0)
Decreased platelet	Grade 3: 25 to < 50 x 10^9/L Grade 4: < 25 x 10^9/L	13 (4.9)	7 (2.6)
Decreased white blood cells	Grade 3: 1.0 to < 2.0 x 10^9/L Grade 4: < 1.0 x 10^9/L	29 (10.9)	32 (12.0)
Serum chemistry			
Decreased calcium	Grade 3: < 7.0 to 6.0 mg/dL Grade 4: < 6.0 mg/dL	3 (1.1)	1 (0.4)
Decreased potassium	Grade 3: < 3.0 to 2.5 mmol/L Grade 4: < 2.5 mmol/L	7 (2.6)	1 (0.4)
Increased alanine aminotransferase	Grade 3: > 5 to 20 x ULN Grade 4: > 20 x ULN	12 (4.5)	0 (0.0)
Increased aspartate aminotransferase	Grade 3: > 5 to 20 x ULN Grade 4: > 20 x ULN	14 (5.2)	2 (0.7)
Increased gamma-glutamyl transferase	Grade 3: > 5 to 20 x ULN Grade 4: > 20 x ULN	8 (3.0)	0 (0.0)
Increased total bilirubin	Grade 3: > 3 to 10 x ULN Grade 4: > 10 x ULN	10 (3.7)	1 (0.4)

Acute Lymphoblastic Leukemia in Pediatric Patients

Table 12. Hematology and Serum Chemistry: Number of pediatric patients experiencing 3 or 4 Grade shifts from baseline after treatment with BLINCYTO (Study MT103-205)

		Pediatric Study (N = 70)	
Laboratory Category Laboratory Parameter	**NCI CTCAE Reference Range Version 4.03 (June 2010)**	**Number of patients with a value change of 3 grade level from baseline, n (%)**	**Number of patients with a value change of 4 grade level from baseline, n (%)**
Hematology			
Decreased absolute lymphocytes	Grade 3: 0.2 to < 0.5 x 10^9/L Grade 4: < 0.2 x 10^9/L	29 (41.4)	11 (15.7)
Decreased absolute neutrophil granulocytes	Grade 3: 0.5 to < 1.0 x 10^9/L Grade 4: < 0.5 x 10^9/L	0 (0.0)	0 (0.0)
Decreased hemoglobin	Grade 3: 65 to < 80 g/L Grade 4: < 65 g/L	10 (14.3)	0 (0.0)
Decreased platelet	Grade 3: 25 to < 50 x 10^9/L Grade 4: < 25 x 10^9/L	4 (5.7)	3 (4.3)
Decreased white blood cells	Grade 3: 1.0 to < 2.0 x 10^9/L Grade 4: < 1.0 x 10^9/L	21 (30.0)	12 (17.1)
Serum chemistry			
Decreased calcium (corrected)	Grade 3: < 7.0 to 6.0 mg/dL Grade 4: < 6.0 mg/dL	0 (0.0)	0 (0.0)
Decreased potassium	Grade 3: < 3.0 to 2.5 mmol/L Grade 4: < 2.5 mmol/L	12 (17.1)	3 (4.3)
Increased alanine aminotransferase	Grade 3: > 5 to 20 x ULN Grade 4: > 20 x ULN	6 (8.6)	1 (1.4)
Increased aspartate aminotransferase	Grade 3: > 5 to 20 x ULN Grade 4: > 20 x ULN	3 (4.3)	1 (1.4)
Increased gamma-glutamyl transferase	Grade 3: > 5 to 20 x ULN Grade 4: > 20 x ULN	0 (0.0)	0 (0.0)
Increased total bilirubin	Grade 3: > 3 to 10 x ULN Grade 4: > 10 x ULN	4 (5.7)	0 (0.0)

8.5 Post-Market Adverse Reactions

Gastrointestinal disorders

Pancreatitis, life-threatening or fatal, has been reported in patients receiving BLINCYTO (see **7 WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**, Pancreatitis).

Nervous system disorders

Cranial nerve disorders, serious events, have been reported in patients receiving BLINCYTO.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

No serious drug interactions have been identified.

9.2 Drug Interactions Overview

No formal drug interaction studies have been conducted with BLINCYTO.

Immunization

The safety of immunization with live viral vaccines during or following BLINCYTO therapy has not been studied.

Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of BLINCYTO treatment, during treatment, and until recovery of B lymphocytes to normal range following the last cycle of BLINCYTO.

9.3 Drug-Behavioural Interactions

No formal drug-behavioural interaction studies have been conducted with BLINCYTO.

9.4 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted with BLINCYTO. Results from *in vitro* testing with human hepatocytes suggested that blinatumomab did not affect CYP450 enzyme activities, thus a pharmacokinetic interaction between blinatumomab and drugs metabolized by CYP450 enzymes is not expected.

Initiation of BLINCYTO treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug-drug interaction risk is during the first 9 days of the first cycle and the first 2 days of the second cycle in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity (eg, warfarin) or drug concentrations (eg, cyclosporine). Adjust the dose of the concomitant drug as needed.

9.5 Drug-Food Interactions

No formal drug-food interaction studies have been conducted with BLINCYTO.

9.6 Drug-Herb Interactions

No formal drug-herb interaction studies have been conducted with BLINCYTO.

9.7 Drug-Laboratory Test Interactions

No formal drug-laboratory interaction studies have been conducted with BLINCYTO.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Blinatumomab is a bispecific T-cell engager (BiTE®) molecule that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. It activates endogenous T cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B cells, including B-precursor ALL cells. The anti-tumour

activity of blinatumomab immunotherapy is not dependent on T cells bearing a specific TCR or on peptide antigens presented by cancer cells, but is polyclonal in nature and independent of human leukocyte antigen (HLA) molecules on target cells. Blinatumomab mediates the formation of a cytolytic synapse between the T-cell and the tumour cell, releasing proteolytic enzymes (such as perforin and granzymes) to kill both proliferating and resting target cells which closely resembles a natural cytotoxic T-cell reaction. Blinatumomab is associated with transient upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T-cells, and results in elimination of CD19+ cells.

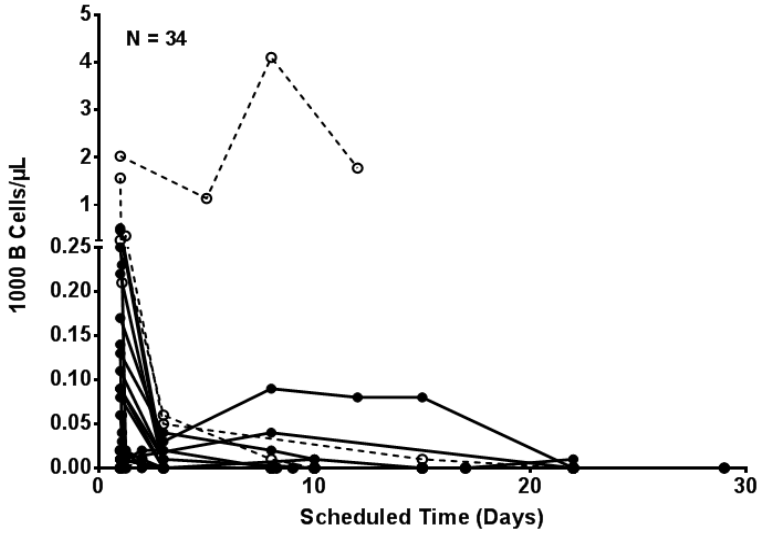
10.2 Pharmacodynamics

Consistent immune-pharmacodynamic responses were observed in the patients studied based on pharmacodynamic measures that include lymphocytes, lymphocyte subsets, and cytokines. During the continuous intravenous infusion over 4 weeks, the pharmacodynamic response was characterized by T-cell activation and initial redistribution, rapid peripheral B-cell depletion, and transient cytokine elevation.

Peripheral T-cell redistribution (i.e., T-cell adhesion to blood vessel endothelium and/or transmigration into tissue) occurred after the start of BLINCYTO infusion or dose escalation. T-cell counts initially declined to very low levels within 1 to 2 days and then returned to baseline levels within 7 to 14 days in the majority of patients. An increase of T-cell counts above baseline (T-cell expansion) was observed in a few patients. Similar dynamic profiles were observed for $CD4^+$ and $CD8^+$ T-cells.

Peripheral B-cell counts decreased rapidly (within two days) to an undetectable level (≤ 10 cells/microliter) during the first treatment cycle at doses ≥ 5 mcg/m^2/day or ≥ 9 mcg/day in the majority of patients (see figure below). For these patients, no recovery of peripheral B-cell counts was observed during the 2-week BLINCYTO-free period between treatment cycles. Incomplete depletion of B-cells occurred at doses of 0.5 mcg/m^2/day and 1.5 mcg/m^2/day and in a few non-responders at higher doses.

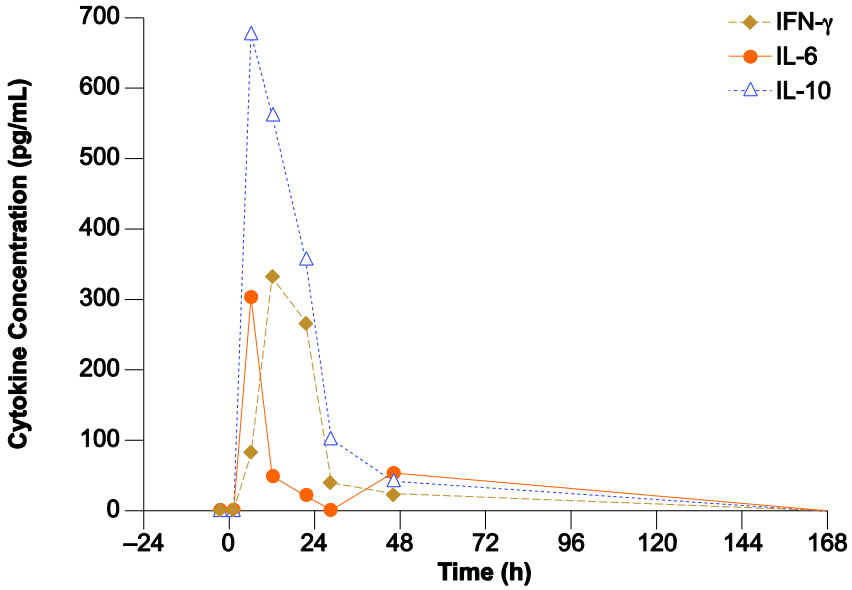
Figure 1. Change of $CD19^+$ B-cell in Peripheral blood During Treatment of Cycle 1



Note: The figure represents individual B-cell counts detected in peripheral blood during the first 28-day continuous blinatumomab intravenous infusion cycle. Lines with closed circles represent patients who achieved a hematological complete remission (CR/CRh*) during the first 2 cycles of blinatumomab treatment; dotted lines with open circles represent patients without CR/CRh* during the first 2 treatment cycles.

Cytokines including IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, TNF-α, and IFN-γ were measured, and IL-6, IL-10, and IFN-γ were more elevated. Transient elevation of cytokines was observed in the first 2 days following the start of BLINCYTO infusion. The elevated cytokine levels returned to baseline within 24 to 48 hours during the infusion (see figure below). In subsequent treatment cycles (see table below), cytokine elevation occurred in fewer patients with lesser intensity compared to the initial 48 hours of the first treatment cycle.

Figure 2. Representative Individual Cytokine Concentration-Time Profiles Following Blinatumomab Continuous IV Infusion



Note: The figure represents cytokine levels measured in serum in an individual in the first week of a 28-day continuous blinatumomab intravenous infusion cycle. IFN-γ=interferon gamma; IL=interleukin

Table 13. Mean (±SD) Serum Cytokine Peak Levels (pg/mL) Following Continuous IV Infusion of Blinatumomab in Patients with R/R ALL

Cycle/ week	Dose (mcg/d)	No. of patients	IL-10 (pg/mL)	IL-6 (pg/mL)	IFN-γ (pg/mL)	IL-2 (pg/mL)	TNF-α (pg/mL)
C1/W1	9	184	589 ± 822	826 ± 2390	93 ± 409	25 ± 45	30 ± 125
C1/W2	28	175	96 ± 136	234 ± 681	27 ± 83	11 ± 5	10 ± 3
C2/W1	28	95	397 ± 633	315 ± 952	23 ± 46	11 ± 5	12 ± 15
C3/W1	28	41	428 ± 941	69 ± 114	22 ± 28	10 ± 2	12 ± 7.8

C = cycle; W=week, IL = interleukin; IFN- γ = interferon gamma; IV = intravenous; R/R ALL = relapsed/refractory acute lymphoblastic leukemia; TNF-α = tumour necrosis factor alpha; SD = standard deviation.

10.3 Pharmacokinetics

Absorption

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 90 mcg/m^2/day (approximately equivalent to 9 to 162 mcg/day) in adult patients. Following continuous intravenous infusion, the steady state serum concentration (C_{ss}) was achieved within a day and remained stable over time. Mean C_{ss} values increased approximately dose

proportionally over the dose range tested. The table below gives the C_{ss} values for patients treated at the clinical doses of 9 mcg/day and 28 mcg/day for the treatment of relapsed or refractory ALL in studies involving Philadelphia chromosome-negative or Philadelphia chromosome-positive patients. PK parameters were estimated by non-compartmental analysis.

The pharmacokinetics of blinatumomab in patients with MRD-positive B-cell precursor ALL were similar to patients with relapsed or refractory ALL.

Table 14. Mean (SD) C_{ss} of Blinatumomab in Subjects with Relapsed/Refractory (R/R) ALL Who Received 9 mcg/day and 28 mcg/day Doses

	Mean (SD) C_{ss} (pg/mL) (n)	
Study (patient population)	**9 mcg/day**	**28 mcg/day**
MT103-211 Ph(-) – R/R ALL	246 (305) (n=178)	632 (510) (n=188)
00103311 Ph(-) – R/R ALL	211 (413) (n=156)	592 (553) (n=191)
20120216 Ph(+) – R/R ALL	155 (106) (n=8)	673 (614) (n=28)
Overall	228 (356) (n=342)	616 (537) (n=407)

ALL = acute lymphoblastic leukemia; Ph(-)=Philadelphia chromosome-negative; Ph(+)=Philadelphia chromosome-positive; C_{ss}=steady state concentration, C_{ss} in cycle 1 of each studies are presented, n = number of subjects; SD = standard deviation.

Distribution:

The estimated mean (SD) volume of distribution based on terminal phase (V_z) was 4.35 (2.45) L with continuous intravenous infusion of blinatumomab, indicating that blinatumomab is mainly distributed in the vascular space. The equivalent value in terms of mL/kg is 61.3 (34.5) mL/kg.

Metabolism:

The metabolic pathway of blinatumomab has not been characterized. Like other protein therapeutics, BLINCYTO is expected to be degraded into small peptides and amino acids via catabolic pathways (eg., taken up by the cells through pinocytosis).

Elimination:

The estimated mean (SD) systemic clearance (CL) and mean (SD) half-life with continuous intravenous infusion in patients receiving blinatumomab in clinical studies was 3.11 (2.98) L/hour and 2.10 (1.41) hours, respectively, showing that blinatumomab is rapidly eliminated from the body upon administration.

Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses. The estimated mean fraction of excreted unchanged blinatumomab in urine was approximately 0.2% at the 60 mcg/m^2/day dose under continuous IV infusion, indicating limited renal excretion of blinatumomab.

Special Populations and Conditions

- **Pediatrics**

  The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 30 mcg/m^2/day in pediatric patients (< 18 years of age). At the recommended doses of 5 and 15 mcg/m^2/day for the treatment of relapsed or refractory B-cell precursor ALL, the mean C_{ss} ± SD were 162 ± 179 and 533 ± 392 pg/mL, respectively. The estimated mean ± SD V_z, CL and terminal half-life ($t_{1/2z}$) were 3.91 ± 3.36 L/m^2, 1.88 ± 1.90 L/hr/m^2 and 2.19 ± 1.53 hours, respectively.

- **Geriatrics**

  A population pharmacokinetic analysis[1] was performed to evaluate the effects of demographic characteristics on blinatumomab pharmacokinetics. Results suggest that age (18 to 80 years of age) does not influence the pharmacokinetics of blinatumomab.

- **Sex**

  A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics on blinatumomab pharmacokinetics. Results suggest that gender does not influence the pharmacokinetics of blinatumomab.

- **Hepatic Insufficiency**

  No formal pharmacokinetic studies of blinatumomab have been conducted in patients with hepatic impairment.

  Results from an *in vitro* test in human hepatocytes suggest that blinatumomab did not affect CYP450 enzyme activities.

  Baseline alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels were used to assess the effect of hepatic impairment on the clearance of blinatumomab with and showed no effect. Further population pharmacokinetic analysis suggested that there was no association between ALT or AST levels and the clearance of blinatumomab.

- **Renal Insufficiency**

  No formal pharmacokinetic studies of blinatumomab have been conducted in patients with renal impairment.

  Pharmacokinetic analyses showed an approximately 2-fold difference in mean blinatumomab clearance values between adult patients with moderate renal dysfunction (CrCL ranging from 30 to 59 mL/min, N = 21) and normal renal function (CrCL more than 90 mL/min, N = 215). However, there was also a high inter-patient variability (CV% up to 96.8%) which minimized the difference between the two groups. There is no information available in patients with severe renal impairment (CrCL < 30 mL/min) or in patients on hemodialysis.

[1] Based on a linear IV infusion model of one-compartment, parameterized in terms of systemic clearance (CL) and volume of distribution for the central compartment (V). Parameters were assumed to be log-normally distributed and an exponential inter-individual variability term was estimated for CL. Residual variability was modeled using an additive error model in the log-domain.

- **Body Weight and Body Surface Area**

  A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics on blinatumomab pharmacokinetics in adults. Results suggest that age (18 to 80 years of age), gender, body weight (39 to 149 kg) and body surface area (1.31 to 2.70 m^2) do not influence the pharmacokinetics of blinatumomab.

  Mean C_{ss} values under the BSA-based (initiate at 5 mcg/m^2/day and step to 15 mcg/m^2/day) and fixed dosing (initiate at 9 mcg/day and step to 28 mcg/day) were similar, supporting the use of a fixed dosing regimen.

11 STORAGE, STABILITY AND DISPOSAL

Protect from light. Do not freeze.

BLINCYTO vial: refrigerate at 2°C to 8°C

IV Solution Stabilizer vial: refrigerate at 2°C to 8°C

Table 15. Storage Requirements for BLINCYTO Vial and Prepared BLINCYTO Infusion Bag

Maximum storage time for lyophilized BLINCYTO vial and IV Solution Stabilizer*	**Maximum storage time of reconstituted BLINCYTO vial***		**Maximum storage time of prepared BLINCYTO Infusion Bag (Preservative-Free)**		**Maximum storage time of prepared BLINCYTO Infusion Bag (with Preservative)**	
Room Temperature 23°C to 27°C	Room Temperature 23°C to 27°C	Refrigerated 2°C to 8°C	Room Temperature 23°C to 27°C	Refrigerated 2°C to 8°C	Room Temperature 23°C to 27°C	Refrigerated 2°C to 8°C
8 hours	4 hours	24 hours	96 hours†	10 days†	7 days†	14 days†

* While stored, protect BLINCYTO vials and IV Solution Stabilizer from light.

† Storage time includes infusion time. If IV bag containing BLINCYTO solution for infusion is not administered within the timeframes and temperatures indicated, it must be discarded; it should not be refrigerated again.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

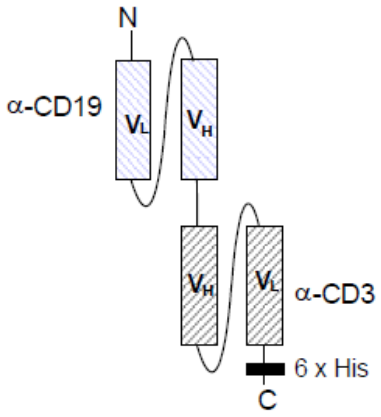
Drug Substance

Proper name: blinatumomab

Molecular formula and molecular mass: blinatumomab consists of 504 amino acids and has a molecular weight of approximately 54 kilodaltons.

Structural formula: BLINCYTO (blinatumomab) is a bispecific T-cell engager (BiTE®) molecule that selectively binds with high affinity to CD19 (expressed on cells of B-lineage origin) and CD3 (expressed on T-cells).

The domain structure of blinatumomab is shown in the figure below.



Product Characteristics: Using recombinant DNA technology, BLINCYTO is produced in a well-characterized mammalian cell (Chinese hamster ovary) culture and is purified by a series of steps that include measures to inactivate and remove viruses.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Acute Lymphoblastic Leukemia in Adult Patients

In **Study 00103311** [A Phase 3, Randomized, Open Label Study Investigating the Efficacy of the BiTE® Antibody Blinatumomab Versus Standard of Care Chemotherapy in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (TOWER Study)], the safety and efficacy of BLINCYTO compared to standard of care (SOC) chemotherapy were evaluated in a randomized, open-label, multicenter study. Eligible patients were ≥ 18 years of age with relapsed or refractory B-cell precursor ALL (had > 5% blasts in the bone marrow and either relapse at any time after allogeneic HSCT, untreated first relapse with first remission duration < 12 months, or refractory to last therapy).

Patients were randomized 2:1 to receive BLINCYTO or 1 of 4 prespecified, investigator-selected, SOC chemotherapy regimens. Randomization was stratified by age (< 35 years vs ≥ 35 years of age), prior salvage therapy (yes versus no), and prior allogeneic HSCT (yes versus no) as assessed at the time of consent. The demographics and baseline characteristics were well-balanced between the two arms (see table below).

Table 16. Demographics and Baseline Characteristics in TOWER Study

Characteristic	BLINCYTO (N = 271[c])	SOC Chemotherapy[a] (N = 134[c])
Age		
Median, years (min, max)	37 (18, 80)	37 (18, 78)
Mean, years (SD)	40.8 (17.1)	41.1 (17.3)
< 35 years, n (%)	123 (45.4)	60 (44.8)
≥ 35 years, n (%)	148 (54.6)	74 (55.2)
≥ 65 Years, n (%)	33 (12.2)	15 (11.2)
≥ 75 Years, n (%)	10 (3.7)	2 (1.5)
Males, n (%)	162 (59.8)	77 (57.5)
Race, n (%)		
American Indian or Alaska Native	4 (1.5)	1 (0.7)
Asian	19 (7.0)	9 (6.7)
Black (or African American)	5 (1.8)	3 (2.2)
Multiple	2 (0.7)	0
Native Hawaiian or Other Pacific Islander	1 (0.4)	1 (0.7)
Other	12 (4.4)	8 (6.0)
White	228 (84.1)	112 (83.6)
Prior salvage therapy	164 (60.5)	80 (59.7)
Prior alloHSCT[b]	94 (34.7)	46 (34.3)
Eastern Cooperative Group Status - n (%)		
0	96 (35.4)	52 (38.8)
1	134 (49.4)	61 (45.5)
2	41 (15.1)	20 (14.9)
Unknown	0	1 (0.7)
Refractory to salvage treatment - n (%)		
Yes	87 (32.1)	34 (25.4)
No	182 (67.2)	99 (73.9)
Unknown	2 (0.7)	1 (0.7)
Maximum of central/local bone marrow blasts - n (%)		
≤ 5%	0	0
> 5 to < 10%	9 (3.3)	7 (5.2)
10 to < 50%	60 (22.1)	23 (17.2)
≥ 50%	201 (74.2)	104 (77.6)
Unknown	1 (0.4)	0

[a] SOC = standard of care

[b] alloHSCT = allogeneic hematopoietic stem cell transplantation

[c] N number under each treatment group represents the number of subjects randomize

BLINCYTO was administered as a continuous intravenous infusion. In the first cycle, the initial dose was 9 mcg/day for week 1, then 28 mcg/day for the remaining 3 weeks. The target dose of 28 mcg/day was administered in cycle 2 and subsequent cycles starting on day 1 of each cycle. Dose adjustment was possible in case of adverse events. Of the 267 patients who received BLINCYTO, the median number of treatment cycles was two (range: 0 to 9 cycles); of the 109 patients who received SOC chemotherapy, the median number of treatment cycles was one (range: 1 to 4 cycles).

In **Study MT103-211** [An Open-label, Multicenter, Phase 2 Study to Evaluate Efficacy and Safety of the Bi-specific T cell Engager (BiTE®) Antibody Blinatumomab in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia], the safety and efficacy of BLINCYTO were evaluated in an open-label, multicenter, single-arm study. Eligible patients were ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (relapsed with first remission duration of ≤ 12 months in first salvage or relapsed or refractory after first salvage therapy or relapsed within 12 months of allogeneic HSCT, and had ≥ 10% blasts in bone marrow). The primary endpoint was the CR/CRh* rate within 2 cycles of treatment with BLINCYTO. Key secondary endpoints were relapse free survival (RFS) and overall survival (OS).

BLINCYTO was administered as a continuous intravenous infusion. In the first cycle, the initial dose was 9 mcg/day for week 1, then 28 mcg/day for the remaining 3 weeks. The target dose of 28 mcg/day was administered in cycle 2 and subsequent cycles starting on day 1 of each cycle. Dose adjustment was possible in case of adverse events. The treated population included 189 patients who received at least 1 infusion of BLINCYTO; the median number of treatment cycles was 2 (range: 1 to 5). Patients who responded to BLINCYTO but later relapsed had the option to be retreated with BLINCYTO. Among treated patients, 70 were female (37%) and 119 were male (63%), the median age was 39 years (range: 18 to 79 years), 64 out of 189 (33.9%) had undergone HSCT prior to receiving BLINCYTO, 77 out of 189 (40.7%) had undergone 1 prior salvage therapy, 42 out of 189 (22.2%) had undergone 2 prior salvage therapies and 32 out of 189 (16.9%) had received more than 2 prior salvage therapies. Sixteen out of 189 (8.5%) patients were primary refractory. Thirty-one out of 189 (16.4%) patients had an ECOG performance status of 2.

In **Study 20120216** [A Phase 2 Single Arm, Multicenter Trial to Evaluate the Efficacy of the BiTE® Antibody Blinatumomab in Adult Subjects With Relapsed/Refractory Philadelphia Positive B-precursor Acute Lymphoblastic Leukemia (ALCANTARA Study)] the safety and efficacy of BLINCYTO were evaluated in an open-label, multicenter, single-arm study. Eligible patients were ≥ 18 years of age with Philadelphia chromosome-positive B-cell precursor ALL, relapsed or refractory to at least 1 second generation or later tyrosine kinase inhibitor (TKI), or intolerant to second generation TKI, and intolerant or refractory to imatinib mesylate.

BLINCYTO was administered as a continuous intravenous infusion. In the first cycle, the initial dose was 9 mcg/day for week 1, then 28 mcg/day for the remaining 3 weeks. The dose of 28 mcg/day was administered in cycle 2 and subsequent cycles starting on day 1 of each cycle. Dose adjustment was possible in case of adverse events. The treated population included 45 patients who received at least one infusion of BLINCYTO; the median number of treatment cycles was 2 (range: 1 to 5).

See table below for the demographics and baseline characteristics from **Study 20120216**.

Table 17. Demographics and Baseline Characteristics in Study 20120216

Characteristic	BLINCYTO (N = 45)
Age	
Median, years (min, max)	55 (23, 78)
Mean, years (SD)	52.8 (15)
≥ 65 Years and < 75 years, n (%)	10 (22.2)
≥ 75 Years, n (%)	2 (4.4)
Males, n (%)	24 (53.3)
Race, n (%)	
Asian	1 (2.2)
Black (or African American)	3 (6.7)
Other	2 (4.4)
White	39 (86.7)
Disease History	
Prior TKI treatment[a], n (%)	
1	7 (15.6)
2	21 (46.7)
≥ 3	17 (37.8)
Prior salvage therapy	31 (61.9)
Prior alloHSCT[b]	20 (44.4)
Bone marrow blasts[c]	
≥ 50% to <75%	6 (13.3)
≥ 75%	28 (62.2)

[a] Number of patients that failed ponatinib = 23 (51.1%)
[b] alloHSCT = allogeneic hematopoietic stem cell transplantation
[c] centrally assessed

In **Study MT103-203** [A Confirmatory Multicenter, Single-arm Study to Assess the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab in Adult Patients With Minimal Residual Disease (MRD) of B-precursor Acute Lymphoblastic Leukemia (BLAST Study)], the safety and efficacy of BLINCYTO were evaluated in an open-label, multicenter, single-arm study. Eligible patients were ≥ 18 years of age, had received at least 3 blocks of standard ALL induction therapy, were in complete hematologic remission (defined as < 5% blasts in bone marrow, absolute neutrophil count ≥ 1,000/µL, platelets ≥ 50,000/µL, and hemoglobin level ≥9 g/dL) and had molecular failure or molecular relapse (defined as MRD ≥ 10^{-3}).

BLINCYTO was administered as a continuous intravenous infusion. Patients received BLINCYTO at a constant dose of 15 mcg/m^2/day (equivalent to the recommended dosage of 28 mcg/day) for all treatment cycles. Patients received up to 4 cycles of treatment. Dose adjustment was possible in case of adverse events. The treated population included 116 patients who received at least one infusion of BLINCYTO. Of the 116 patients, 113 patients (97.4%) were included in the primary endpoint full analysis set and 110 patients (94.8%) were included in the key secondary endpoint full analysis set which excludes the Ph-positive subjects. The median number of treatment cycles was 2 (range: 1 to 4). Please see table below for the demographics and baseline characteristics from Study MT103-203.

Table 18. Demographics and Baseline Characteristics in Study MT103-203

Characteristic	BLINCYTO (N = 116)
Age	
Median, years (min, max)	45 (18, 76)
Mean, years (SD)	44.6 (16.4)
≥ 65 years, n (%)	15 (12.9)
Males, n (%)	68 (58.6)
Race, n (%)	
Asian	1 (0.9)
Other (mixed)	1 (0.9)
White	102 (87.9)
Unknown	12 (10.3)
Philadelphia chromosome disease status	
Positive	5 (4.3)
Negative	111 (95.7)
Relapse history	
Patients in 1st CR	75 (64.7)
Patients in 2nd CR	39 (33.6)
Patients in 3rd CR	2 (1.7)
MRD level at baseline*	
$\geq 10^{-1}$ and < 1	9 (7.8)
$\geq 10^{-2}$ and < 10^{-1}	45 (38.8)
$\geq 10^{-3}$ and < 10^{-2}	52 (44.8)
< 10^{-3}	3 (2.6)
Below Lower Limit of Quantification	5 (4.3)
Unknown	2 (1.7)

* Centrally assessed in an assay with minimum sensitivity of 10^{-4}

Acute Lymphoblastic Leukemia in Pediatric Patients

The safety and efficacy of BLINCYTO were evaluated in an open-label, multicenter, single-arm Phase I/II study in 93 pediatric patients (< 18 years of age) with relapsed or refractory B-cell precursor ALL (Study MT103-205). Eligible patients had second or later bone marrow relapse, any marrow relapse after allogeneic HSCT, or were refractory to other treatments had > 25% blasts in bone marrow as determined by a central laboratory and had Karnofsky performance status of ≥ 50% (patients ≥ 16 years of age) or Lansky performance status of ≥ 50% (patients < 16 years of age).

Patients were excluded if they had active acute or extensive chronic graft-versus-host disease (GvHD) including taking immunosuppressive agents to prevent or treat GvHD within 2 weeks before BLINCYTO treatment; known or suspected central nervous (CNS) involvement by ALL; history of or current relevant CNS pathology; HSCT within 3 months before BLINCYTO treatment; immediately previous cancer chemotherapy, radiotherapy, or immunotherapy.

The recommended dose for this study was determined to be 5 mcg/m^2/day on Days 1-7 and 15 mcg/m^2/day on Days 8-28 for cycle 1, and 15 mcg/m^2/day on Days 1-28 for subsequent cycles. The treated population included 70 patients who received at least one infusion of BLINCYTO at this recommended dose; the median number of treatment cycles was one (range: 1 to 5).

Among treated patients, the median age was 8 years (range: 7 months to 17 years), 40 out of 70 (57.1%) had undergone allogeneic HSCT prior to receiving BLINCYTO, and 39 out of 70 (55.7%) had refractory disease. Most patients (52/70) had a high tumour burden (≥ 50% leukemic blasts in bone marrow) at baseline with a median of 75.5% bone marrow blasts.

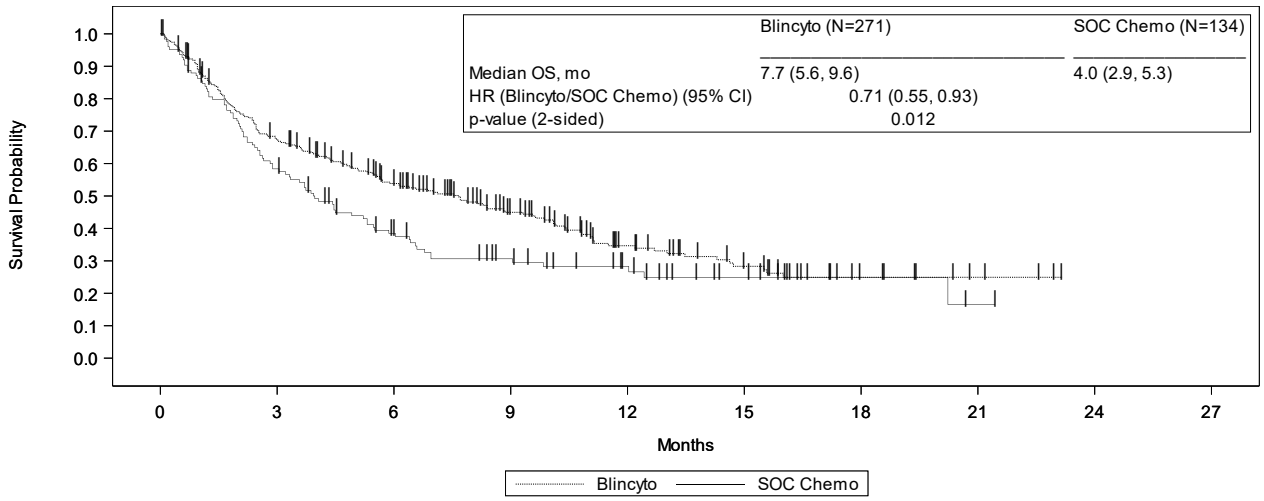
The primary endpoint was complete remission (CR) rate, which was defined as the rate of M1 bone marrow (≤ 5% blasts in the bone marrow) with no evidence of circulating blasts or extra-medullary disease within the first two cycles of BLINCYTO treatment. In this study, pediatric patients did not need to recover their peripheral blood counts in order to achieve a CR.

14.2 Study Results

Acute Lymphoblastic Leukemia in Adult Patients

In the TOWER Study, the primary endpoint was overall survival (OS). The study demonstrated statistically significant improvement in OS for patients treated with BLINCYTO as compared to SOC chemotherapy (the hazard ratio [95% CI] was 0.71 [0.55, 0.93], a p-value = 0.012). In patients with 0 prior salvage therapies the hazard ratio for OS was 0.60 (0.39, 0.91), in patients with one prior salvage therapy the hazard ratio for OS was 0.59 (0.38, 0.91), and in patients with more than two prior salvage therapies the hazard ratio for OS was 1.13 (0.64, 1.99). OS benefit was independent of transplant; consistent results were observed after censoring at the time of HSCT. See figure and table below for efficacy results from TOWER Study.

Figure 3. Kaplan-Meier Curve of Overall Survival (TOWER Study)



Number of Subjects at Risk

Blincyto	271	176	124	79	45	27	9	4	0	0
SOC Chemo	134	71	41	27	17	7	4	1	0	0

A censored subject is indicated by a Vertical Bar |.

Table 19. Efficacy Results in Patients ≥ 18 Years of Age with Philadelphia Chromosome-negative Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia (ALL) (TOWER Study)

	BLINCYTO (N = 271)	SOC Chemotherapy (N = 134)
Overall Survival		
Median, months [95% CI]	7.7 (5.6, 9.6)	4.0 (2.9, 5.3)
Hazard Ratio [95% CI][a]	0.71 (0.55, 0.93)	
p-value[b]	0.012	
Complete Remission (CR)		
CR[c]/CRh*[d]/CRi[e], n (%) [95% CI]	119 (43.9) (37.9, 50)	33 (24.6) (17.6, 32.8)
Treatment difference [95% CI]	19.3 (9.9, 28.7)	
p-value[b]	< 0.001	
CR, n (%) [95% CI]	91 (33.6) (28.0, 39.5)	21 (15.7) (10, 23)
Treatment difference [95% CI]	17.9 (9.6, 26.2)	
p-value[f]	< 0.001	
Duration of CR/CRh*/CRi[g]		
Median, months [95% CI]	7.3 (5.8, 9.9)	4.6 (1.8, 19)
Event-free Survival[h]		
6-month estimate % [95% I]	30.7 (25, 36.5)	12.5 (7.2, 19.2)
Hazard Ratio [95% CI]	0.55 (0.43, 0.71)	
MRD Response[i] for CR/CRh*/CRi		
n1/n2 (%)[j] [95% CI]	74/97 (76.3) (66.6, 84.3)	16/33 (48.5) (30.8, 66.5)

a Based on stratified Cox's model.

b The p-value was derived using stratified log-rank test.

c CR was defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).

d CRh* (complete remission with partial hematologic recovery) was defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).

e CRi (complete remission with incomplete hematologic recovery) was defined as ≤ 5% blasts in the bone marrow, no evidence of disease, and incomplete recovery of peripheral blood counts (platelets > 100,000/microliter or ANC > 1,000/microliter).

f The p-value was derived using Cochran-Mantel-Haenszel test

g Duration of CR/CRh*/CRi was defined as time since first response to relapse or death, whichever is earlier. Relapse was defined as hematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.

h EFS time was calculated from the time of randomization until the date of disease assessment indicating a relapse after achieving a CR/CRh*/CRi or death, whichever is earlier. Subjects who fail to achieve a CR/CRh*/CRi within 12 weeks of treatment initiation are considered treatment failures and assigned an EFS duration of 1 day.

i MRD (minimum residual disease) response was defined as MRD by PCR or flow cytometry < 1 x 10^{-4}.

j n1: number of patients who achieved MRD response and CR/CRh*/CRi; n2: number of patients who achieved CR/CRh*/CRi.

In **Study MT103-211**, eighty-one out of 189 (42.9%) patients achieved CR/CRh* within the first 2 treatment cycles with the majority of responses (64 out of 81) occurring within cycle 1 of treatment. See table below for efficacy results. Of the 18 patients who achieved CRh*, 3 patients achieved CR during consolidation cycles. Thirty-two out of 189 (16.9%) patients underwent allogeneic HSCT in CR/CRh* induced with BLINCYTO. Numerically, patients with prior allogeneic HSCT had similar response rates to those without prior HSCT, and older patients had similar response rates to younger patients.

Table 20. Efficacy Results in Patients ≥ 18 Years of Age with Philadelphia Chromosome-negative Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia (ALL) (Study MT103-211)

	N =189
Complete remission (CR)[a]/Complete remission with partial hematological recovery (CRh*)[b], n (%) [95% CI]	81 (42.9%) [35.7% – 50.2%]
CR, n (%) [95% CI]	63 (33.3%) [26.7% – 40.5%]
CRh*, n (%) [95% CI]	18 (9.5%) [5.7% – 14.6%]

a. CR was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).

b. CRh* was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).

In **Study 20120216**, the primary endpoint was the CR/CRh* rate within two cycles of treatment with BLINCYTO. Sixteen out of 45 (35.6%) patients achieved CR/CRh* within the first two treatment cycles. See table below for efficacy results from Study 20120216.

Two patients achieved CR during subsequent cycles, resulting in a cumulative CR rate of 35.6% (16 out of 45; 95% CI: 21.9 – 51.2). Five out of 16 (31.3%) patients underwent allogeneic HSCT in CR/CRh* induced with BLINCYTO.

Table 21. Efficacy Results in Patients ≥ 18 Years of Age With Philadelphia Chromosome-positive Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia (ALL) (Study 20120216)

	N = 45
Complete remission (CR)[a]/Complete remission with partial hematological recovery (CRh*)[b], n (%) [95% CI]	16 (35.6) [21.9, 51.2]
CR, n (%) [95% CI]	14 (31.1) [18.2, 46.6]
CRh*, n (%) [95% CI]	2 (4.4) [0.5, 15.1]
Median Relapse[c]-free survival (RFS) for CR/CRh* [95% CI]	6.7 months [4.4 to NE[d]]

a CR was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).

b CRh* was defined as ≤ 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).

c Relapse was defined as hematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse

d NE = not estimable

Treatment effects in evaluable subgroups (e.g., mutation status, number of prior TKIs, prior HSCT status, and relapse without prior HSCT) were in general consistent with the results in the overall population. Patients with T315I mutation, other mutations, or additional cytogenetic abnormalities responded with a similar rate as compared to those that did not have these mutations or abnormalities.

In **Study MT103-203**, the primary endpoint was the proportion of patients who achieved complete MRD response within one cycle of BLINCYTO treatment. Eighty-eight out of 113 (77.9%) patients achieved a complete MRD response after one cycle of treatment. In patients with Philadelphia chromosome negative B-precursor ALL, the 18-month KM estimate for hematological Relapsed-Free Survival, censored at HSCT or post-blinatumomab chemotherapy, was 54% (95% CI: 33, 70). MRD response rates by age and MRD level at baseline subgroups were consistent with the results in the overall population. See table below for efficacy results from Study MT103-203.

Table 22. Efficacy Results in Patients ≥ 18 Years of Age With MRD-positive B-cell Precursor Acute Lymphoblastic Leukemia (ALL) (Study MT103-203)

Complete MRD response[a], n/N (%), [95% CI]	88/113 (77.9) [69.1, 85.1]
Patients in 1st CR, n/N (%), [95% CI]	60/73 (82.2) [71.5, 90.2]
Patients in 2nd CR, n/N (%), [95% CI]	27/38 (71.1) [54.1, 84.6]
Duration of complete MRD response	17.3 months [12.6 to 23.3]

[a] Complete MRD response was defined as the absence of detectable MRD confirmed in an assay with minimum sensitivity of 10^{-4}

Acute Lymphoblastic Leukemia in Pediatric Patients

Twenty-seven out of 70 patients (38.6%) achieved the primary endpoint (see table below). Thirteen of the 27 patients (48.1%) who achieved the primary endpoint received an allogeneic HSCT. Ten of 18 patients (55.6%) with < 50% blasts at baseline achieved a CR compared to 17 of 52 patients (32.7%) with ≥ 50% blasts at baseline. The CR for patients less than 2 years of age was 60% (6/10), for patients 2 to 6 years was 40.0% (8/20); and for patients aged 7 to 17 years was 32.5% (13/40).

Table 23. Efficacy Results in Patients < 18 Years of Age with Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia (ALL) (Study MT103-205)

	N = 70
CR[a], n (%) [95% CI]	**27 (38.6%) [27.2% – 51.0%]**
CR with full recovery of peripheral blood counts[b]	12 (17.1%) [9.2% – 28.0%]
CR with partial recovery of peripheral blood counts[c]	11 (15.7%) [8.1% – 26.4%]
CR without a partial recovery of peripheral blood counts[d]	4 (5.7%) [1.6%- 14.0%]
Median Relapse[e]-free survival (RFS) [95% CI]	4.4 months [2.3 - 12.1 months]

a. CR was defined as M1 marrow (≤ 5% of blasts in the bone marrow) and no evidence of circulating blasts or extra-medullary

b. CR with full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).

c. CR with partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).

d. CR without a partial recovery of peripheral blood counts (platelets ≤ 50,000/microliter and/or ANC ≤ 500/microliter).

e. Relapse was defined as hematological relapse (blasts in bone marrow greater than 25% following CR) or an extramedullary relapse

14.3 Comparative Bioavailability Studies

Not Applicable

14.4 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of BLINCYTO has been evaluated using an electrochemiluminescence detection technology (ECL) screening immunoassay for the detection of binding anti-blinatumomab antibodies. For patients whose sera tested positive in the screening immunoassay, an *in vitro* biological assay was performed to detect neutralizing antibodies.

In the clinical studies of adult ALL patients treated with BLINCYTO, less than 2% tested positive for anti-blinatumomab antibodies. Of patients who developed anti-blinatumomab antibodies, the majority had *in vitro* neutralizing activity.

Anti-blinatumomab antibody formation may affect the pharmacokinetics of BLINCYTO.

No anti-blinatumomab antibodies were detected in clinical studies of pediatric patients (N = 93) with relapsed or refractory ALL treated with BLINCYTO.

If formation of anti-blinatumomab antibodies with a clinically significant effect is suspected, contact Amgen at 1-866-502-6436 to discuss antibody testing.

The detection of anti-blinatumomab antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to blinatumomab with the incidence of antibodies to other products may be misleading.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Blinatumomab only cross-reacts in the chimpanzee. Consequently, preclinical safety data with blinatumomab are limited. Findings from mouse studies up to 13 weeks with a surrogate molecule were limited to the expected pharmacology.

Carcinogenicity:

No carcinogenicity studies have been conducted with blinatumomab.

Genotoxicity:

No mutagenicity studies have been conducted with blinatumomab.

Reproductive and Developmental Toxicology:

No studies have been conducted to evaluate the effects of blinatumomab on fertility. There were no effects on male or female reproductive organ weights, gross observations or histopathology in mice treated for 13-weeks with a surrogate molecule.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrBLINCYTO® (blin sye' toe)

blinatumomab

Read this carefully before you start taking **BLINCYTO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **BLINCYTO**.

Serious Warnings and Precautions

BLINCYTO can cause serious side effects that can be severe, life-threatening, or lead to death, including:

- Cytokine Release Syndrome and Infusion Reactions (fever, tiredness or weakness, dizziness, headache, low blood pressure, nausea, vomiting, chills, face swelling, wheezing or trouble breathing and skin rash).
- Tumour Lysis Syndrome (complications occurring after cancer treatment leading to increased blood levels of potassium, uric acid, and phosphorus and decreased blood levels of calcium).
- Neurological problems (disturbances of brain function such as difficulty in communicating, tingling of skin, seizure, difficulty thinking or processing thoughts, difficulty remembering).
- Infections (fever, aches, feeling tired, cough).
- Pancreatitis (inflammation of the pancreas) that includes symptoms of severe and persistent stomach pain, with or without nausea and vomiting.

What is BLINCYTO used for?

For the following indications BLINCYTO has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- Treatment of Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia who have detectable traces of cancer cells (referred to as minimal residual disease positive or MRD-positive) after treatment with chemotherapy.
- Treatment of pediatric patients with Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia that has come back after a previous treatment (relapsed) or if there was no response to the first treatment (refractory).

For the following indication BLINCYTO has been approved without conditions. This means it has passed Health Canada's review and can be bought and sold in Canada.

- Treatment of acute lymphoblastic leukemia in adults that has come back after a previous treatment (relapsed) or if there was no response to the first treatment (refractory). Acute lymphoblastic leukemia is a cancer of the blood in which a particular kind of white blood cell is growing out of control. Acute lymphoblastic leukemia is also referred to as ALL.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does BLINCYTO work?

BLINCYTO helps your immune system destroy a particular kind of white blood cell, which are the cancer cells in acute lymphoblastic leukemia.

What are the ingredients in BLINCYTO?

Medicinal ingredients: blinatumomab

Non-medicinal ingredients: citric acid monohydrate, lysine hydrochloride, polysorbate 80, sodium hydroxide and trehalose dihydrate.

BLINCYTO is sold with a vial containing a liquid that will be used by the healthcare professional to prepare your dose of BLINCYTO. It contains the following non-medicinal ingredients: citric acid monohydrate, lysine hydrochloride, polysorbate 80, sodium hydroxide and water for injection.

BLINCYTO comes in the following dosage forms:

BLINCYTO is sold as a lyophilized powder in a vial. One vial contains 38.5 micrograms of powder for solution for infusion. Each package of BLINCYTO also contains a vial of liquid that will be used by the healthcare professional to prepare your dose of BLINCYTO.

Do not use BLINCYTO if:

- you are allergic to blinatumomab or to any of the ingredients of BLINCYTO.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BLINCYTO. Talk about any health conditions or problems you may have, including if you:

- have a history of radiation treatment to the brain, or chemotherapy treatment.
- have a history of neurological problems, for example, shaking (or tremor), abnormal sensations, seizures, memory loss, confusion, disorientation, loss of balance, or difficulty in speaking. If you are still suffering from active neurological problems or conditions, tell your doctor. If your leukemia has spread to your brain and/or spinal cord, your doctor may have to treat this first before you can start treatment with BLINCYTO. Your doctor will assess your nervous system and conduct tests before deciding if you should receive BLINCYTO. Your doctor may need to take special care of you during your treatment with BLINCYTO.
- have an infection;

- have ever had an infusion reaction after receiving BLINCYTO or other medications. Symptoms may include wheezing, flushing, face swelling, difficulty breathing, low or high blood pressure;
- have severe and persistent stomach pain, with or without nausea and vomiting, as these may be symptoms of a serious and potentially fatal condition known as pancreatitis (inflammation of the pancreas);
- are pregnant or plan to become pregnant. BLINCYTO may harm your unborn baby. Tell your healthcare professional if you become pregnant during treatment with BLINCYTO. Women who are able to become pregnant should use contraception during treatment. You must also do this for 48 hours after your last treatment. Talk to your healthcare professional about suitable methods of contraception;
- become pregnant during BLINCYTO treatment, your doctor may need to talk to you about precautions in using vaccinations for your baby;
- are breastfeeding or plan to breastfeed. It is not known if BLINCYTO passes into your breast milk. You should not breast-feed during treatment with BLINCYTO and for at least 48 hours after your last treatment. You and your healthcare professional should decide if you will take BLINCYTO or breastfeed. You should not do both.

Other warnings you should know about:

Your doctor will order blood tests to check your liver function before you start BLINCYTO and during treatment with BLINCYTO.

Before each infusion cycle of BLINCYTO, you will be given medicines which help reduce a potentially life-threatening complication known as tumour lysis syndrome, which is caused by chemical disturbances in the blood due to the breakdown of dying cancer cells.

During treatment, especially in the first few days after treatment start, you may experience a severe low white blood cell count (neutropenia), severe low white blood cell count with a fever (febrile neutropenia), elevated liver enzymes, or elevated uric acid. Your doctor will take regular blood tests to monitor your blood counts during treatment with BLINCYTO.

Do not drive, operate heavy machinery, or do other dangerous activities while you are receiving BLINCYTO because BLINCYTO can cause neurological symptoms such as dizziness, seizures, and confusion.

Benzyl alcohol preservative toxicity

If you are prescribed 7-day bags of BLINCYTO solution for infusion, they will contain benzyl alcohol as a preservative. Serious side effects (e.g., gasping syndrome) including death have happened in newborns or infants who have received benzyl alcohol intravenously. Seven-day bags of BLINCYTO solution for infusion are not recommended for use in patients weighing less than 22 kg (48 lbs).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

Tell your healthcare professional if you think you or your child receiving BLINCYTO may need any vaccinations in the near future, including those needed to travel to other countries. Some vaccines must not be given within two weeks before, at the same time as or in the months after you receive treatment with BLINCYTO. Your doctor will check if you should have the vaccination.

The following may interact with BLINCYTO:

- It is not known which medications interact with BLINCYTO.

How to take BLINCYTO:

BLINCYTO will be given to you by a healthcare professional in a healthcare setting.

- Before you receive BLINCYTO, you will be given a medicine (corticosteroid) to help reduce side effects (infusion reactions and cytokine release syndrome). The amount of medicine and length of treatment will depend on your age and how much cancer you have (tumour burden).
- BLINCYTO will be given to you by infusion into your vein by a pump.
- You will receive BLINCYTO by continuous infusion into your vein for 4 weeks (28 days), followed by a 2-week break (14 days) during which you will not be given BLINCYTO. This is one treatment cycle (42 days). After the 2-week break, your healthcare professional will decide if you will be treated with more cycles of BLINCYTO.
- Your healthcare professional may change your dose of BLINCYTO, delay, or completely stop treatment with BLINCYTO if you have certain side effects.
- Your healthcare professional will do blood tests during treatment with BLINCYTO to check you for side effects.
- It is very important to keep the area around the IV catheter clean to reduce the risk of getting an infection. Your healthcare professional will show you how to care for your catheter site.
- Do not change the settings on your infusion pump, even if there is a problem with your pump or your pump alarm sounds. Any changes to your infusion pump settings may cause a dose that is too high or too low to be given.

Call your healthcare professional right away if you have any problems with the pump or the pump alarm sounds, if the infusion bag empties before the scheduled bag change or if the infusion pump stops unexpectedly.

Treatment of Relapsed or Refractory B-cell precursor ALL

Your healthcare professional should give you BLINCYTO in a hospital or clinic for the first 9 days of the first treatment cycle and for the first 2 days of the second cycle to check you for side effects. If you receive additional treatment cycles of BLINCYTO or if your treatment is stopped for a period of time and restarted, you may also be treated in a hospital or clinic.

Treatment of MRD-positive B-cell Precursor ALL

Your healthcare professional should give you BLINCYTO in a hospital or clinic for the first 3 days of your first treatment cycle and the first 2 days of your second cycle to check you for side effects.

Usual Dose:

Treatment of Relapsed or Refractory B-cell precursor ALL

Patients weighing 45 kilograms or more

You will be given 9 micrograms per day of BLINCYTO for the first week of your first cycle. You will be given 28 micrograms per day for the rest of the first cycle and for all other cycles. Your doctor will determine if more cycles should be given or if your dose should change.

You may not be able to tell the difference between the 9 micrograms per day and 28 micrograms per day infusions.

Patients weighing less than 45 kilograms

Your pump will be set to deliver a dose based on your body size (surface area). You will be given 5 micrograms per square meter per day for the first week of your first cycle. You will be given 15 micrograms per square meter per day for the rest of the first cycle (days 8 - 28) and for all other cycles. Your doctor will determine if more cycles should be given or if your dose should change.

You may not be able to tell the difference between the 5 micrograms per square meter per day and the 15 micrograms per square meter per day infusions.

Treatment of MRD-positive B-cell Precursor ALL

Patients weighing 45 kilograms or more

You will be given 28 micrograms per day of BLINCYTO for all treatment cycles. Your pump will be set to deliver a dose of 28 micrograms per day. Your doctor will determine the number of cycles of BLINCYTO that should be given.

Patients weighing less than 45 kilograms

You will be given 15 micrograms per square meter per day for all treatment cycles. Your pump will be set to deliver a dose based on your body size (surface area). Your doctor will determine the number of cycles of BLINCYTO that should be given.

Overdose:

If you think you, or a person you are caring for, have taken too much BLINCYTO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Speak with your healthcare professional as soon as possible if you miss a dose of BLINCYTO.

What are possible side effects from using BLINCYTO:

These are not all the possible side effects you may have when taking BLINCYTO. If you experience any side effects not listed here, tell your healthcare professional. Please also see **Warnings and Precautions**.

Very common side effects (may affect more than 1 in 10 people):

- infections in the blood including bacteria, fungi, viruses, or infections in other organs
- low levels of certain white blood cells with fever (febrile neutropenia), decreased levels of red blood cells (anemia), decreased levels of white blood cells (neutropenia, leukopenia), decreased levels of platelets (thrombocytopenia)
- fever, swelling, chills, decreased or increased blood pressure and fluid in the lungs, which may become severe (cytokine release syndrome)
- sleep problems (insomnia)
- headache
- rapid heart rate (tachycardia)
- low blood pressure
- cough
- rash
- back pain, bone pain
- fever (pyrexia), swelling of hands, ankles or feet
- high levels of liver enzymes (ALT, AST)
- reactions related to infusion may include, wheezing, flushing, face swelling, difficulty breathing, low blood pressure, high blood pressure

Common side effects (may affect up to 1 in 10 people):

- high white blood cell counts, low levels of certain white blood cells (lymphopenia), swollen lymph nodes
- pain in extremity, chills, chest pain
- complications during or after cancer treatment leading to high blood levels of potassium, uric acid, and phosphorus and low blood levels of calcium (tumour lysis syndrome)
- confusion, disorientation
- shaking (or tremor), dizziness, drowsiness (somnolence), disturbances of brain function (encephalopathy) such as difficulty in communicating (aphasia), tingling of skin (paresthesia), reduced pain or touch sensation (hypoesthesia), seizure, difficulty thinking or processing thoughts, difficulty remembering
- high blood pressure (hypertension), flushing
- wet cough, shortness of breath (dyspnea)
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (allergic reaction)
- low levels of antibodies called “immunoglobulins” which help the immune system fight against infections (decreased immunoglobulins)
- high levels of bilirubin and liver enzymes (GGT)
- overdose

Uncommon side effects (may affect up to 1 in 100 people):

- a condition which causes fluid to leak from the small blood vessels into your body (capillary leak syndrome)
- fever, swelling, chills, decreased or increased blood pressure and fluid in the lungs, which may be severe and can be fatal (cytokine storm)
- nerve problems affecting the head and neck such as visual disturbances, difficulty with facial movements, difficulty hearing, and trouble swallowing (cranial nerve disorders)

Some side effects more frequently seen in adolescents and children include:

- runny nose (rhinitis)
- low phosphorus levels in blood (hypophosphatemia), low calcium levels in blood (hypocalcemia)
- nose bleeds (epistaxis)
- high levels of the enzyme lactate dehydrogenase (LDH) in blood

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Cytokine Release Syndrome and Infusion Reactions (fever, tiredness or weakness, dizziness, headache, low blood pressure, nausea, vomiting, chills, face swelling, wheezing or trouble breathing and skin rash)		✓	
Infections (fever, aches, feeling tired, cough)		✓	
COMMON			
Tumour lysis syndrome (complications occurring after cancer treatment leading to increased blood levels of potassium, uric acid, and phosphate and decreased blood levels of calcium)		✓	
Neurological problems (seizures, difficulty in speaking or slurred speech, loss of consciousness, confusion and disorientation and loss of balance)		✓	
UNCOMMON			
Capillary leak syndrome (a condition which causes fluid to leak from the small blood vessels into your body)		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

BLINCYTO will be prepared in a bag for intravenous infusion by a healthcare professional. Intravenous bags containing BLINCYTO will be stored in the refrigerator at 2°C to 8°C for up to 10 days (preservative-free bag) and for up to 14 days (with preservative).

Do not throw away (dispose of) any BLINCYTO in your household trash. Talk with your healthcare professional about disposal of BLINCYTO and used supplies.

Keep out of reach and sight of children.

If you want more information about BLINCYTO:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.amgen.ca, or by calling 1 866-502-6436.

This leaflet was prepared by Amgen Canada Inc.

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