FULL PRESCRIBING INFORMATION
BLINCYTO® Powder for Infusion 35 mcg/vial

1 INDICATIONS AND USAGE

1.1 MRD-positive B-cell Precursor ALL

BLINCYTO is indicated for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults and children.

1.2 Relapsed or Refractory B-cell Precursor ALL

BLINCYTO is indicated for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.

2 DOSAGE AND ADMINISTRATION

In patients with a history or presence of clinically relevant central nervous system (CNS) pathology *[see Warnings and Precautions (5.2)]*, hospitalization is recommended at a minimum for the first 14 days of the first cycle. In the second cycle, hospitalization is recommended at a minimum for 2 days, and clinical judgment should be based on tolerance to BLINCYTO in the first cycle. Caution should be exercised as cases of late occurrence of first neurological events in the second cycle have been observed.

For all subsequent cycle starts and reinitiation (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended.

2.1 Treatment of MRD-positive B-cell Precursor ALL

- A treatment course consists of 1 cycle of BLINCYTO for induction followed by up to 3 additional cycles for consolidation.

- A single cycle of treatment of BLINCYTO induction or consolidation consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days).

- See Table 1 for the recommended dose by patient weight and schedule. Patients weighing 45 kg or more receive a fixed-dose. For patients weighing less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

Table 1. Recommended BLINCYTO Dose and Schedule for the Treatment of MRD-positive B-cell Precursor ALL

Cycle	**Patients Weighing 45 kg or More** ***(Fixed-dose)***	**Patients Weighing Less Than 45 kg** ***(BSA-based dose)***
Induction Cycle 1		
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 2-4		
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

- Hospitalization is recommended 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-initiations (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended.
- Premedicate with prednisone or equivalent for MRD-positive B-cell Precursor ALL
    - 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 in each cycle.
    - For pediatric patients, premedicate with 5 mg/m^2 of dexamethasone, to a maximum dose of 20 mg, 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.
- For administration of BLINCYTO:
    - See Section 2.5 for infusion over 24 hours ,48 hours, 72 hours, or 96 hours.

2.2 Treatment of Relapsed or Refractory B-cell Precursor ALL

- A treatment course consists of up to 2 cycles of BLINCYTO for induction followed by 3 additional cycles for consolidation and up to 4 additional cycles of continued therapy.
- A single cycle of treatment of BLINCYTO induction or consolidation consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days).
- A single cycle of treatment of BLINCYTO continued therapy consists of 28 days of continuous intravenous infusion followed by a 56-day treatment-free interval (total 84 days).
- See Table 2 for the recommended dose by patient weight and schedule. Patients weighing 45 kg or more receive a fixed-dose and for patients weighing less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

Table 2. Recommended BLINCYTO Dose and Schedule for the Treatment of Relapsed or Refractory B-cell Precursor ALL

Cycle	**Patients Weighing 45 kg or More** ***(Fixed-dose)***	**Patients Weighing 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 Days 29-42	28 mcg/day 14-day treatment-free interval	15 mcg/m^2/day *(not to exceed 28 mcg/day)* 14-day treatment-free interval
Consolidation Cycles 3-5 Days 1-28 Days 29-42	28 mcg/day 14-day treatment-free interval	15 mcg/m^2/day *(not to exceed 28 mcg/day)* 14-day treatment free interval
Continued Therapy Cycles 6-9 Days 1-28 Days 29-84	28 mcg/day 56-day treatment-free interval	15 mcg/m^2/day *(not to exceed 28 mcg/day)* 56-day treatment-free interval

- Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiation (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended.
- Premedicate with dexamethasone.
    - For adult patients, premedicate with 20 mg of dexamethasone intravenously 1 hour prior to the first dose of BLINCYTO of each cycle, prior to a step dose (such as Cycle 1 Day 8), and when restarting an infusion after an interruption of 4 or more hours.
    - For pediatric patients, premedicate with dexamethasone 10mg/m^2 (not to exceed 20mg) orally or intravenously 6 to 12 hours prior to the start of Blincyto (Cycle 1 day 1), followed by dexamethasone 5mg/m^2 (not to exceed 20mg) orally or intravenously within 30 minutes prior to the start of Blincyto (Cycle 1 day 1), prior to a step dose (such as Cycle 1 day 8), and when restarting an infusion after an interruption of 4 or more hours in the first cycle.
- For administration of BLINCYTO:
    - See Section 2.5 for infusion over 24 hours, 48 hours, 72 hours or 96 hours.

- 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.

2.3 Dosage Modifications for Adverse Reaction

If the interruption after an adverse reaction is no longer than 7 days, 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 reaction is longer than 7 days, start a new cycle.

Table 3. Dosage Modifications for Adverse Reactions

Adverse Reaction	Grade*	Patients Weighing 45 kg or More	Patients Weighing Less Than 45 kg
Cytokine Release Syndrome (CRS)	Grade 3	• Interrupt BLINCYTO • Administer dexamethasone 8 mg every 8 hours intravenously or orally for up to 3 days and taper thereafter over 4 days. • When CRS is resolved, restart BLINCYTO at 9 mcg/day, and escalate to 28 mcg/day after 7 days if the adverse reaction does not recur.	• Interrupt BLINCYTO • Administer dexamethasone 5mg/m^2 (maximum 8mg) every 8 hours intravenously or orally for up to 3 days and taper thereafter over 4 days. • When CRS is resolved, restart BLINCYTO at 5 mcg/m^2/day, and escalate to 15 mcg/m^2/day after 7 days if the adverse reaction does not recur.
	Grade 4	Discontinue BLINCYTO permanently. Administer dexamethasone as instructed for Grade 3 CRS.	
Neurological Toxicity	Seizure	Discontinue BLINCYTO permanently if more than one seizure occurs.	
	Grade 3	Withhold 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 adverse reaction does not recur. If the adverse reaction occurred at 9 mcg/day, or if the adverse reaction takes more than 7 days to resolve, discontinue BLINCYTO permanently.	Withhold 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 adverse reaction does not recur. If the adverse reaction occurred at 5 mcg/m^2/day, or if the adverse reaction takes more than 7 days to resolve, discontinue BLINCYTO permanently.

Adverse Reaction	Grade*	Patients Weighing 45 kg or More	Patients Weighing Less Than 45 kg
	Grade 4	Discontinue BLINCYTO permanently.	
Other Clinically Relevant Adverse Reactions	Grade 3	Withhold 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 adverse reaction does not recur. If the adverse reaction takes more than 14 days to resolve, discontinue BLINCYTO permanently.	Withhold 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 adverse reaction does not recur. If the adverse reaction 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.

2.4 Preparation

It is very important that the instructions for preparation (including admixing) and administration provided in this section are strictly followed to minimize medication errors (including underdose and overdose) *[see Warnings and Precautions (5.13)]*.

BLINCYTO can be infused over 24 hours, 48 hours, 72 hours or 96 hours. The choice between these options for the infusion duration should be made by the treating healthcare provider considering the frequency of the infusion bag changes and the weight of the patient.

For preparation, reconstitution, and administration of BLINCYTO:

- See Section 2.5 for infusion over 24 hours, 48 hours, 72 hours or 96 hours.

2.4.1 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:

- Prepare BLINCYTO in a USP <797> compliant facility.
- Prepare BLINCYTO in an ISO Class 5 laminar flow hood or better.
- Ensure that the admixing area has appropriate environmental specifications, confirmed by periodic monitoring.
- Ensure that personnel are appropriately trained in aseptic manipulations and admixing of oncology drugs.
- Ensure that personnel wear appropriate protective clothing and gloves.
- Ensure that gloves and surfaces are disinfected.

2.4.2 Package Content

1 package 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.

2.4.3 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/pump cassettes.
- Use polyolefin, PVC DEHP-free, or EVA intravenous tubing sets.

2.5 Preparation and Administration of BLINCYTO as a 24 Hour, 48 Hour, 72 Hour or 96 Hour Infusion

Reconstitute BLINCYTO with preservative-free Sterile Water for Injection, USP. 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 Injection, USP.

2.5.1 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, USP** 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, colorless to slightly yellow.
    - Do not use if solution is cloudy or has precipitated.

2.5.2 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 45 kg or more
- Table 5 for patients weighing less than 45 kg

1. Aseptically **add 270 mL 0.9% Sodium Chloride Injection, USP** to the empty intravenous bag.
2. Aseptically **transfer 5.5 mL IV Solution Stabilizer** to the intravenous bag containing 0.9% Sodium Chloride Injection, USP. 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 Injection, USP and IV Solution Stabilizer. Gently mix the contents of the bag to avoid foaming.
    - Refer to Table 4 for patients weighing 45 kg or more 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 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 Dosage and Administration (2.7)]*.

Table 4. For Patients Weighing 45 kg or More: Volumes to Add to Intravenous Bag

0.9% Sodium Chloride Injection, USP (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 Injection, USP (starting volume)				270 mL	
IV Solution Stabilizer (fixed volume for 24, 48, 72 and 96 hour infusion)				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

0.9% Sodium Chloride Injection, USP (starting volume)	270 mL
IV Solution Stabilizer (fixed volume for 24, 48, 72 and 96 hour infusion)	5.5 mL

Infusion Duration	**Dose**	**Infusion Rate**	**BSA (m^2)**	**Reconstituted BLINCYTO**	
				Volume	**Vials**
			0.4 – 0.49	0.59 mL	1
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

0.9% Sodium Chloride Injection, USP (starting volume)	270 mL
IV Solution Stabilizer (fixed volume for 24, 48, 72 and 96 hour infusion)	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
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

0.9% Sodium Chloride Injection, USP (starting volume)	270 mL
IV Solution Stabilizer (fixed volume for 24, 48, 72 and 96 hour infusion)	5.5 mL

Infusion Duration	**Dose**	**Infusion Rate**	**BSA (m^2)**	**Reconstituted BLINCYTO**	
				Volume	**Vials**
			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

2.5.3 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
  - Infusion rate of 3.3 mL/hour for a duration of 72 hours
  - 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 micron in-line filter.
- **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.

2.6 Storage Requirements of Reconstituted BLINCYTO

The information in Table 6 indicates the storage time for the reconstituted BLINCYTO vial and prepared infusion bag.

Table 6. Storage Time for Reconstituted BLINCYTO Vial and Prepared BLINCYTO Infusion Bag

	Maximum Storage Time	
	Room Temperature up to 27°C	Refrigerated 2°C to 8°C
Reconstituted BLINCYTO Vial	4 hours	24 hours
Prepared BLINCYTO Infusion Bag	96 hours*	10 days

* Storage time includes infusion time. If the prepared BLINCYTO infusion bag is not administered within the time frames and temperatures indicated, it must be discarded; it should not be refrigerated again.

3 DOSAGE FORMS AND STRENGTHS

For infusion: 35 mcg of white to off-white lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

BLINCYTO is contraindicated in patients with known hypersensitivity to blinatumomab or to any component of the product formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. The median time to onset of CRS was 2 days after the start of infusion and the median time to resolution of CRS was 5 days among cases that resolved. Manifestations of CRS include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased total bilirubin, and disseminated intravascular coagulation (DIC). The manifestations of CRS after treatment with BLINCYTO overlap with those of infusion reactions, capillary leak syndrome (CLS), and hemophagocytic histiocytosis/macrophage activation syndrome (MAS). Using all of these terms to define CRS in clinical trials of BLINCYTO, CRS was reported in 15% of patients with relapsed or refractory ALL and in 7% of patients with MRD-positive ALL *[see Adverse Reactions (6.1)]*.

Monitor patients for signs or symptoms of these events. Advise outpatients on BLINCYTO to contact their healthcare professional for signs and symptoms associated with CRS. If severe CRS occurs, interrupt BLINCYTO until CRS resolves. Discontinue BLINCYTO permanently if life-threatening CRS occurs. Administer corticosteroids for severe or life-threatening CRS *[see Dosage and Administration (2.3)]*.

5.2 Neurological Toxicities

In patients with ALL receiving BLINCYTO in clinical studies, neurological toxicities have occurred in approximately 65% of patients *[see Adverse Reactions (6.1)]*. Among patients that experienced a neurologic event, the median time to the first event was within the first 2 weeks of BLINCYTO treatment and the majority of events resolved. The most common (≥ 10%) manifestations of neurological toxicity were headache and tremor; the neurological toxicity profile varied by age group *[see Use in Specific Populations (8.4, 8.5)]*. Grade 3 or higher (severe, life-threatening, or fatal) neurological toxicities following initiation of BLINCYTO administration occurred in approximately 13% of patients and included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Manifestations of neurological toxicity included cranial nerve disorders. The majority of neurologic events resolved following interruption of BLINCYTO, but some resulted in treatment discontinuation.

Elderly patients experienced a higher rate of neurological toxicities, including cognitive disorder, encephalopathy, and confusion.

Patients with a medical history of neurologic signs and symptoms (such as dizziness, hypoesthesia, hyporeflexia, tremor, dysesthesia, paresthesia, memory impairment) demonstrated a higher rate of neurologic events (such as tremor, dizziness, confusional state, encephalopathy, and ataxia). The median time to onset of a neurologic event in these patients was 12 days.

There is limited experience in patients with a history or presence of clinically relevant central nervous system (CNS) pathology (e.g., epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis) as they were excluded from

clinical trials. There is a possibility of a higher risk of neurologic events in this population. The potential benefits of treatment should be carefully weighed against the risk of neurologic events and heightened caution should be exercised when administering BLINCYTO to these patients.

There is limited experience with blinatumomab in patients with documented active ALL in the central nervous system (CNS) or cerebrospinal fluid (CSF). However patients have been treated with blinatumomab in clinical studies after clearance of CSF blasts with CNS directed therapy (such as intrathecal chemotherapy). Therefore once the CSF is cleared, treatment with BLINCYTO may be initiated.

Monitor patients receiving BLINCYTO for signs and symptoms of neurological toxicities. Advise outpatients on BLINCYTO to contact their healthcare professional if they develop signs or symptoms of neurological toxicities. Interrupt or discontinue BLINCYTO as recommended *[see Dosage and Administration (2.3)]*.

5.3 Infections

In patients with ALL receiving BLINCYTO in clinical studies, serious infections such as sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site infections were observed in approximately 25% of patients, some of which were life-threatening or fatal *[see Adverse Reactions (6.1)]*. As appropriate, administer prophylactic antibiotics and employ surveillance testing during treatment with BLINCYTO. Monitor patients for signs and symptoms of infection and treat appropriately. Management of infections may require either temporary interruption or discontinuation of Blincyto *[see Dosage and Administration (2.3)]*.

Patients with Eastern Cooperative Oncology Group (ECOG) performance status at baseline of 2 experienced a higher incidence of serious infections compared to patients with ECOG performance status of < 2. There is limited experience with BLINCYTO in patients with an active uncontrolled infection.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), which may be life-threatening or fatal, has been observed in patients receiving BLINCYTO *[see Adverse Reactions (6.1)]*. Appropriate prophylactic measures, including pretreatment nontoxic cytoreduction and on-treatment hydration, should be used for the prevention of TLS during BLINCYTO treatment. Monitor for signs or symptoms of TLS. Management of these events may require either temporary interruption or discontinuation of BLINCYTO *[see Dosage and Administration (2.3)]*.

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 showed an increased incidence of TLS compared with patients with mild renal impairment or normal renal function.

5.5 Neutropenia and Febrile Neutropenia

Neutropenia and febrile neutropenia, including life-threatening cases, have been observed in patients receiving BLINCYTO *[see Adverse Reactions (6.1)]*. Monitor laboratory parameters (including, but not limited to, white blood cell count and absolute neutrophil count) during BLINCYTO infusion. Interrupt BLINCYTO if prolonged neutropenia occurs.

5.6 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 Warnings and Precautions (5.2)]*. 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.

5.7 Elevated Liver Enzymes

Treatment with BLINCYTO was associated with transient elevations in liver enzymes *[see Adverse Reactions (6.1)]*. In patients with ALL receiving BLINCYTO in clinical studies, the median time to onset of elevated liver enzymes was 3 days.

The majority of these transient elevations in liver enzymes were observed in the setting of CRS. For the events that were observed outside the setting of CRS, the median time to onset was 19 days. Grade 3 or greater elevations in liver enzymes occurred in approximately 7% of patients outside the setting of CRS and resulted in treatment discontinuation in less than 1% of patients.

Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during BLINCYTO treatment. Interrupt BLINCYTO if the transaminases rise to greater than 5 times the upper limit of normal or if total bilirubin rises to more than 3 times the upper limit of normal.

5.8 Pancreatitis

Fatal pancreatitis has been reported in patients receiving BLINCYTO in combination with dexamethasone in clinical studies and the postmarketing setting *[see Adverse Reactions (6.3)]*.

Evaluate patients who develop signs and symptoms of pancreatitis. Management of pancreatitis may require either temporary interruption or discontinuation of BLINCYTO and dexamethasone *[see Dosage and Administration (2.3)]*.

5.9 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 antileukemic 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).

5.10 CD19-Negative Relapse

CD19-negative B-precursor ALL has been reported in relapsed patients receiving BLINCYTO. Particular attention should be given to assessment of CD19 expression at the time of bone marrow testing.

5.11 Lineage Switch from ALL to Acute Myeloid Leukemia (AML)

Lineage switch from ALL to AML has been rarely reported in relapsed patients receiving BLINCYTO, including those with no immunophenotypic and/or cytogenetic abnormalities at initial diagnosis. All relapsed patients should be monitored for presence of AML.

5.12 Infusion Reactions

Infusion reactions have occurred with the BLINCYTO infusion and may be clinically indistinguishable from manifestations of CRS.

The infusion reactions were generally rapid, occurring within 48 hours after initiating infusion. However, some patients reported delayed onset of infusion reactions or in later cycles. Patients should be observed closely for infusion reactions, especially during the initiation of the first and second treatment cycles and treated appropriately. Anti-pyretic use (e.g., paracetamol) is recommended to help reduce pyrexia during the first 48 hours of each cycle.

5.13 Preparation and Administration Errors

Preparation and administration errors have occurred with BLINCYTO treatment. Follow instructions for preparation (including admixing) and administration strictly to minimize medication errors (including underdose and overdose) *[see Dosage and Administration (2.4)]*.

5.14 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 immune recovery following last cycle of BLINCYTO.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome *[see Warnings and Precautions (5.1)]*
- Neurological Toxicities *[see Warnings and Precautions (5.2)]*
- Infections *[see Warnings and Precautions (5.3)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.4)]*
- Neutropenia and Febrile Neutropenia *[see Warnings and Precautions (5.5)]*
- Effects on Ability to Drive and Use Machines *[see Warnings and Precautions (5.6)]*
- Elevated Liver Enzymes *[see Warnings and Precautions (5.7)]*
- Pancreatitis *[see Warnings and Precautions (5.8)]*
- Leukoencephalopathy *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

MRD-positive B-cell Precursor ALL

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 reactions that occurred within 30 days of the end of BLINCYTO treatment (atypical pneumonia and subdural hemorrhage).

Table 7 summarizes the adverse reactions occurring at a ≥ 10% incidence for any grade or ≥ 5% incidence for Grade 3 or higher.

Table 7. 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

Adverse Reaction	**BLINCYTO (N=137)**	
	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)

Table 7. 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

Adverse Reaction	BLINCYTO (N=137)	
	Any Grade* n (%)	Grade ≥ 3* n (%)
Psychiatric disorders		
Insomnia[11]	24 (18)	1 (<1)
Respiratory, thoracic and mediastinal disorders		
Cough	18 (13)	0 (0)
Skin and subcutaneous tissue disorders		
Rash[12]	22 (16)	1 (<1)
Vascular disorders		
Hypotension	19 (14)	1 (<1)

* Grading based on NCI Common Terminology Criteria 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.

Additional adverse reactions in patients with MRD-positive ALL that did not meet the threshold criteria for inclusion in Table 7 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

Philadelphia Chromosome-negative Relapsed or Refractory B-cell Precursor ALL

The safety of BLINCYTO was evaluated in a randomized, open-label, active-controlled clinical study (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 was 37 years (range: 18 to 80 years), 60% were male, 84% were White, 7% Asian, and 2% were Black or African American 2% were American Indian or Alaska Native, and 5% were Multiple/Other.

The most common adverse reactions (≥ 20%) in the BLINCYTO arm were infections (bacterial and pathogen unspecified), pyrexia, headache, infusion-related reactions, anemia, febrile neutropenia, thrombocytopenia, and neutropenia. Serious adverse reactions were reported in 62% of patients. The most common serious adverse reactions (≥ 2%) included febrile neutropenia, pyrexia, sepsis, pneumonia, overdose, septic shock, CRS, bacterial sepsis, device related infection, and bacteremia. Adverse reactions of Grade 3 or higher were reported in 87% of patients. Discontinuation of therapy due to adverse reactions occurred in 12% of patients treated with BLINCYTO; neurologic events and infections were the most frequently reported reasons for discontinuation of treatment due to an adverse reaction. Fatal adverse events occurred in 16% of patients. The majority of the fatal events were infections.

The adverse reactions occurring at a ≥ 10% incidence for any grade or ≥ 5% incidence for Grade 3 or higher in the BLINCYTO-treated patients in first cycle of therapy are summarized in Table 8.

Table 8. Adverse Reactions Occurring at ≥ 10% Incidence for Any Grade or ≥ 5% Incidence for Grade 3 or Higher in BLINCYTO-treated Patients in First Cycle of Therapy

Adverse Reaction	BLINCYTO (N = 267)		Standard of Care (SOC) Chemotherapy (N = 109)	
	Any Grade* n (%)	Grade ≥ 3* n (%)	Any Grade* n (%)	Grade ≥ 3* n (%)
Blood and lymphatic system disorders				
Neutropenia[1]	84 (31)	76 (28)	67 (61)	61 (56)
Anemia[2]	68 (25)	52 (19)	45 (41)	37 (34)
Thromobocytopenia[3]	57 (21)	47 (18)	42 (39)	40 (37)
Leukopenia[4]	21 (8)	18 (7)	9 (8)	9 (8)
Cardiac disorders				
Arrhythmia[5]	37 (14)	5 (2)	18 (17)	0 (0)
General disorders and administration site conditions				
Pyrexia	147 (55)	15 (6)	43 (39)	4 (4)
Edema[6]	48 (18)	3 (1)	20 (18)	1 (1)
Immune system disorders				
Cytokine release syndrome[7]	37 (14)	8 (3)	0 (0)	0 (0)
Infections and infestations				
Infections - pathogen unspecified	74 (28)	40 (15)	50 (46)	35 (32)
Bacterial infectious disorders	38 (14)	19 (7)	35 (32)	21 (19)
Viral infectious disorders	30 (11)	4 (1)	14 (13)	0 (0)

Fungal infectious disorders	27 (10)	13 (5)	15 (14)	9 (8)
Injury, poisoning and procedural complications				
Infusion-related reaction[8]	79 (30)	9 (3)	9 (8)	1 (1)
Investigations				
Hypertransaminasemia[9]	40 (15)	22 (8)	13 (12)	7 (6)
Nervous system disorders				
Headache	61 (23)	1 (<1)	30 (28)	3 (3)
Skin and subcutaneous tissue disorders				
Rash[10]	31 (12)	2 (1)	21 (19)	0 (0)

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

1 Neutropenia includes agranulocytosis, febrile neutropenia, neutropenia, and neutrophil count decreased

2 Anemia includes anemia and hemoglobin decreased

3 Thrombocytopenia includes platelet count decreased and thrombocytopenia

4 Leukopenia includes leukopenia and white blood cell count decreased

5 Arrhythmia includes arrhythmia, atrial fibrillation, atrial flutter, bradycardia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, and tachycardia

6 Edema includes face edema, fluid retention, edema, edema peripheral, peripheral swelling, and swelling face

7 Cytokine release syndrome includes cytokine release syndrome and cytokine storm

8 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: pyrexia, cytokine release syndrome, hypotension, myalgia, acute kidney injury, hypertension, and rash erythematous

9 Hypertransaminasemia includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased

10 Rash includes erythema, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash pruritic, skin exfoliation, and toxic skin eruption.

Selected laboratory abnormalities worsening from baseline Grade 0-2 to treatment-related maximal Grade 3-4 in first cycle of therapy are shown in Table 9.

Table 9. Selected Laboratory Abnormalities Worsening from Baseline Grade 0-2 to Treatment-related Maximal Grade 3-4[*] in First Cycle of Therapy

	BLINCYTO Grade 3 or 4 (%)	**SOC Chemotherapy** Grade 3 or 4 (%)
Hematology		
Decreased lymphocyte count	80	83
Decreased white blood cell count	53	97
Decreased hemoglobin	29	43
Decreased neutrophil count	57	68
Decreased platelet count	47	85
Chemistry		
Increased ALT	11	11
Increased bilirubin	5	4
Increased AST	8	4

[*] Includes only patients who had both baseline and at least one laboratory measurement during first cycle of therapy available.

Relapsed or Refractory B-cell Precursor ALL

Other important adverse reactions from pooled relapsed or refractory B-cell precursor ALL studies were:

Blood and lymphatic system disorders: lymphadenopathy, hematophagic histiocytosis, and leukocytosis (includes leukocytosis and white blood cell count increased)
General disorders and administration site conditions: chills, chest pain (includes chest discomfort, chest pain, musculoskeletal chest pain, and non-cardiac chest pain), pain, body temperature increased, hyperthermia, and systemic inflammatory response syndrome
Hepatobiliary disorders: hyperbilirubinemia (includes blood bilirubin increased and hyperbilirubinemia)
Immune system disorders: hypersensitivity (includes hypersensitivity, anaphylactic reaction, angioedema, dermatitis allergic, drug eruption, drug hypersensitivity, erythema multiforme, and urticaria)
Injury, poisoning and procedural complications: medication error and overdose (includes overdose, medication error, and accidental overdose)
Investigations: weight increased, decreased immunoglobulins (includes immunoglobulins decreased, blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, and hypogammaglobulinemia), blood alkaline phosphatase increased, and hypertransaminasemia
Metabolism and nutrition disorders: tumor lysis syndrome
Musculoskeletal and connective tissue disorders: back pain, bone pain, and pain in extremity
Nervous system disorders: tremor (resting tremor, intention tremor, essential tremor, and tremor), altered state of consciousness (includes altered state of consciousness, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, stupor, and somnolence), dizziness, memory impairment, seizure (includes seizure, and atonic seizure), aphasia, cognitive disorder, speech disorder, hypoesthesia, encephalopathy, paresthesia, and cranial nerve disorders (trigeminal neuralgia, trigeminal nerve disorder, sixth nerve paralysis, cranial nerve disorder, facial nerve disorder, and facial paresis).
Psychiatric disorders: insomnia, disorientation, confusional state, and depression (includes depressed mood, depression, suicidal ideation, and completed suicide)
Respiratory, thoracic and mediastinal disorders: dyspnea (includes acute respiratory failure, dyspnea, dyspnea exertional, respiratory failure, respiratory distress, bronchospasm, bronchial hyperreactivity, tachypnea, and wheezing), cough, and productive cough
Vascular disorders: hypotension (includes blood pressure decreased, hypotension, hypovolemic shock, and circulatory collapse), hypertension (includes blood pressure increased, hypertension, and hypertensive crisis), flushing (includes flushing and hot flush), and capillary leak syndrome

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of 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.

The immunogenicity of BLINCYTO has been evaluated using either an electrochemiluminescence detection technology (ECL) or an enzyme-linked immunosorbent assay (ELISA) 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 clinical studies, less than 2% of patients treated with BLINCYTO tested positive for binding anti-blinatumomab antibodies. Of patients who developed anti-blinatumomab antibodies, 7 out of 9 (78%) had *in vitro* neutralizing activity. Anti-blinatumomab antibody formation may affect pharmacokinetics of BLINCYTO.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post approval use of BLINCYTO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Fatal pancreatitis, has been reported in patients receiving BLINCYTO in combination with dexamethasone.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with BLINCYTO. 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 (e.g., warfarin) or drug concentrations (e.g., cyclosporine). Adjust the dose of the concomitant drug as needed *[see Clinical Pharmacology (12.2, 12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BLINCYTO may cause fetal harm, including B-cell lymphocytopenia when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no data on the use of BLINCYTO in pregnant women. In animal reproduction studies, a murine surrogate molecule administered to pregnant mice crossed the placental barrier *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Clinical Considerations

Fetal/Neonatal adverse reactions
Due to the potential for B-cell lymphocytopenia in infants following exposure to BLINCYTO in-utero, the infant's B lymphocytes should be monitored before the initiation of live virus vaccination. *[see Warnings and Precautions (5.14)]*.

Data

Animal Data
Animal reproduction studies have not been conducted with blinatumomab. In embryo-fetal developmental toxicity studies, a murine surrogate molecule was administered intravenously to pregnant mice during the period of organogenesis. The surrogate molecule crossed the placental barrier and did not cause embryo-fetal toxicity or teratogenicity. The expected depletions of B and T cells were observed in the pregnant mice, but hematological effects were not assessed in fetuses.

8.2 Lactation

Risk Summary

There is no information regarding the presence of blinatumomab in human milk, the effects on the breastfed infant, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breastfed infants from BLINCYTO, including B-cell lymphocytopenia, advise patients not to breastfeed during treatment with BLINCYTO and for at least 48 hours after the last dose.

8.3 Females and Males of Reproductive Potential

BLINCYTO may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating BLINCYTO treatment.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with BLINCYTO and for at least 48 hours after the last dose.

8.4 Pediatric Use

The safety and efficacy of BLINCYTO have been established in pediatric patients with relapsed or refractory B-cell precursor ALL. Use of BLINCYTO is supported by a single-arm trial in pediatric patients with relapsed or refractory B- cell precursor ALL. This study included pediatric patients in the following age groups: 10 infants (1 month up to less than 2 years), 40 children (2 years up to less than 12 years), and 20 adolescents (12 years to less than 18 years). No differences in efficacy were observed between the different age subgroups. The efficacy has also been established based on extrapolation from adequate and well-controlled studies in adults with MRD-positive B-cell precursor ALL.

In general, the adverse reactions in BLINCYTO-treated pediatric patients were similar in type to those seen in adult patients with relapsed or refractory B-cell precursor ALL *[see Adverse Reactions (6.1)]*. Adverse reactions that were observed more frequently (≥ 10% difference) in the pediatric population compared to the adult population were pyrexia (80% vs. 61%), hypertension (26% vs. 8%), anemia (41% vs 24%), infusion-related reaction (49% vs. 34%), thrombocytopenia (34% vs.21%), leukopenia (24% vs. 11%), and weight increased (17% vs. 6%).

In pediatric patients less than 2 years old (infants), the incidence of neurologic toxicities was not significantly different than for the other age groups, but its manifestations were different; the only event terms reported were agitation, headache, insomnia, somnolence, and irritability. Infants also had an increased incidence of hypokalemia (50%) compared to other pediatric age cohorts (15-20%) or adults (17%).

The steady-state concentrations of blinatumomab were comparable in adult and pediatric patients at the equivalent dose levels based on BSA-based regimens.

8.5 Geriatric Use

Of the total number of patients with ALL treated in clinical studies of BLINCYTO, approximately 12% were 65 and over while 2% were 75 and older. No overall differences in safety or effectiveness were observed between these patients and younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, elderly patients experienced a higher rate of serious infections and neurological toxicities, including cognitive disorder, encephalopathy, and confusion *[see Warnings and Precautions (5.2, 5.3)]*.

10 OVERDOSAGE

Overdoses have been observed, including one adult patient who received 133-fold the recommended therapeutic dose of BLINCYTO delivered over a short duration.

In the dose evaluation phase of a study in pediatric and adolescent patients with relapsed or refractory B-cell precursor ALL, 1 patient experienced a fatal cardiac failure event in the setting of life-threatening cytokine release syndrome (CRS) at a 30 mcg/m^2/day (higher than the maximum tolerated/recommended) dose *[see Warnings and Precautions (5.1) and Adverse Reactions (6)]*.

Overdoses resulted in adverse reactions which were consistent with the reactions observed at the recommended dosage and included fever, tremors, and headache. In the event of overdose, interrupt the infusion, monitor the patient for signs of adverse reactions, and provide supportive care *[see Warnings and Precautions (5.13)]*. Consider re-initiation of BLINCYTO at the recommended dosage when all adverse reactions have resolved and no earlier than 12 hours after interruption of the infusion *[see Dosage and Administration (2.1)]*.

11 DESCRIPTION

Blinatumomab is a bispecific CD19-directed CD3 T-cell engager. Blinatumomab is produced in Chinese hamster ovary cells. It consists of 504 amino acids and has a molecular weight of approximately 54 kilodaltons.

Each BLINCYTO package contains 1 vial BLINCYTO and 1 vial IV Solution Stabilizer.

BLINCYTO (blinatumomab) for injection is supplied in a single-dose vial as a sterile, preservative-free, white to off-white lyophilized powder for intravenous use. Each single-dose vial of BLINCYTO contains 35 mcg blinatumomab, citric acid monohydrate (3.35 mg), lysine hydrochloride (23.23 mg), polysorbate 80 (0.64 mg), trehalose dihydrate (95.5 mg), and sodium hydroxide to adjust pH to 7.0. After reconstitution with 3 mL of preservative-free Sterile Water for Injection, USP, the resulting concentration is 12.5 mcg/mL blinatumomab.

IV Solution Stabilizer is supplied in a single-dose vial as a sterile, preservative-free, colorless to slightly yellow, clear solution. Each single-dose vial of IV Solution Stabilizer contains citric acid monohydrate (52.5 mg), lysine hydrochloride (2283.8 mg), polysorbate 80 (10 mg), sodium hydroxide to adjust pH to 7.0, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Blinatumomab is a bispecific CD19-directed CD3 T-cell engager that binds 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. Blinatumomab mediates the formation of a synapse between the T cell and the tumor cell, upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, which result in redirected lysis of CD19+ cells.

12.2 Pharmacodynamics

During the continuous intravenous infusion over 4 weeks, the pharmacodynamic response was characterized by T-cell activation and initial redistribution, reduction in peripheral B cells, and transient cytokine elevation.

Peripheral T cell redistribution (ie, T cell adhesion to blood vessel endothelium and/or transmigration into tissue) occurred after start of BLINCYTO infusion or dose escalation. T cell counts initially declined within 1 to 2 days and then returned to baseline levels within 7 to 14 days in the majority of patients. Increase of T cell counts above baseline (T cell expansion) was observed in few patients.

Peripheral B cell counts decreased to less than or equal to 10 cells/microliter during the first treatment cycle at doses $\geq$ 5 mcg/m^2/day or $\geq$ 9 mcg/day in the majority of 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 patients at higher doses.

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 elevated. The highest elevation of cytokines was observed in the first 2 days following start of BLINCYTO infusion. The elevated cytokine levels returned to baseline within 24 to 48 hours during the infusion. In subsequent treatment cycles, cytokine elevation occurred in fewer patients with lesser intensity compared to the initial 48 hours of the first treatment cycle.

12.3 Pharmacokinetics

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 (Css) was achieved within a day and remained stable over time. The increase in mean Css values was approximately proportional to the dose in the range tested. At the clinical doses of 9 mcg/day and 28 mcg/day for the treatment of relapsed or refractory ALL, the mean (SD) Css was 228 (356) pg/mL and 616 (537) pg/mL, respectively.

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.

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.

Elimination
The estimated mean (SD) systemic clearance with continuous intravenous infusion in patients receiving blinatumomab in clinical studies was 3.11 (2.98) L/hour. The mean (SD) half-life was 2.10 (1.41) hours. Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses.

Gender, Age, and Body Surface Area
Results of population pharmacokinetic analyses indicate that age (0.62 to 80 years of age) and gender do not influence the pharmacokinetics of blinatumomab. Body surface area (0.4 to 2.70 m^2) influences the pharmacokinetics of blinatumomab, however, the clinical relevance of this effect is unknown.

Hepatic Impairment
No formal pharmacokinetic studies using BLINCYTO have been conducted in patients with hepatic impairment.

Renal Impairment
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 patients with moderate renal impairment (CrCL ranging from 30 to 59 mL/min, N = 21) and normal renal function (CrCL more than 90 mL/min, N = 215). However, high interpatient variability was discerned (CV% up to 96.8%), and clearance values in renal impaired patients were essentially within the range observed in patients with normal renal function. There is no information available in patients with severe renal impairment (CrCL less than 30 mL/min) or patients on hemodialysis.

Drug Interactions
Transient elevation of cytokines may suppress CYP450 enzyme activities *[see Drug Interactions (7) and Clinical Pharmacology (12.2)]*.

Specific Populations

Pediatrics

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 30 mcg/m^2/day in pediatric patients. 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 (SD) steady-state concentration (C_{ss}) values were 162 (179) and 533 (392) pg/mL, respectively. The estimated mean (SD) volume of distribution (V_z), clearance (CL), and terminal half-life ($t_{1/2,z}$) in Cycle 1 were 3.91 (3.36) L/m^2, 1.88 (1.90) L/hour/m^2 and 2.19 (1.53) hours, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with blinatumomab.

No studies have been conducted to evaluate the effects of blinatumomab on fertility. A murine surrogate molecule had no adverse effects on male and female reproductive organs in a 13-week repeat-dose toxicity study in mice.

14 CLINICAL STUDIES

14.1 MRD-positive B-cell Precursor ALL

BLAST Study

The efficacy of BLINCYTO was evaluated in an open-label, multicenter, single-arm study (BLAST Study) that included patients who were ≥ 18 years of age, had received at least 3 chemotherapy blocks of standard ALL therapy, were in hematologic complete remission (defined as < 5% blasts in bone marrow, absolute neutrophil count > 1 Gi/L, platelets > 100 Gi/L) and had MRD at a level of ≥ 0.1% using an assay with a minimum sensitivity of 0.01%. BLINCYTO was administered at a constant dose of 15 mcg/m^2/day (equivalent to the recommended dosage of 28 mcg/day) intravenously 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 86 patients in first or second hematologic complete remission (CR1 or CR2). The demographics and baseline characteristics are shown in Table 10. The median number of treatment cycles was 2 (range: 1 to 4). Following treatment with BLINCYTO, 45 out of 61 (73.8%) patients in CR1 and 14 out of 25 (56.0%) patients in CR2 underwent allogeneic hematopoietic stem cell transplantation in continuous hematologic complete remission.

Table 10. Demographics and Baseline Characteristics in BLAST Study

Characteristics	BLINCYTO (N = 86)
Age	
Median, years (min, max)	43 (18,76)
≥ 65 years, n (%)	10 (12)
Males, n (%)	50 (58)
Race, n (%)	
Asian	1 (1)
Other (mixed)	0 (0)
White	76 (88)
Unknown	9 (11)
Philadelphia chromosome disease status, n (%)	
Positive	1 (1)
Negative	85 (99)
Relapse history, n (%)	
Patients in 1st CR	61 (71)
Patients in 2nd CR	25 (29)
MRD level at baseline*, n (%)	

Table 10. Demographics and Baseline Characteristics in BLAST Study

Characteristics	BLINCYTO (N = 86)
≥ 10%	7 (8)
≥ 1% and < 10%	34 (40)
≥ 0.1% and < 1%	45 (52)

* Assessed centrally using an assay with minimum sensitivity of 0.01%.

Efficacy was based on achievement of undetectable MRD within one cycle of BLINCYTO treatment and hematological relapse-free survival (RFS). The assay used to assess MRD response had a sensitivity of 0.01% for 6 patients and ≤ 0.005% for 80 patients. Overall, undetectable MRD was achieved by 70 patients (81.4%: 95% CI: 71.6%, 89.0%). The median hematological RFS was 22.3 months. Table 11 shows the MRD response and hematological RFS by remission number.

Table 11. Efficacy Results in Patients ≥ 18 Years of Age with MRD-positive B-cell Precursor ALL (BLAST Study)

	Patients in CR1 (n=61)	Patients in CR2 (n=25)
Complete MRD response[1], n (%), [95% CI]	52 (85.2) [73.8, 93.0]	18 (72.0) [50.6, 87.9]
Median hematological relapse-free survival[2] in months (range)	35.2 (0.4, 53.5)	12.3 (0.7, 42.3)

1. Complete MRD response was defined as the absence of detectable MRD confirmed in an assay with minimum sensitivity of 0.01%
2. Relapse was defined as either hematological or extramedullary relapse, secondary leukemia, or death due to any cause; Includes time after transplantation; Kaplan Meier estimate

Undetectable MRD was achieved by 65 of 80 patients (81.3%: 95% CI: 71.0%, 89.1%) with an assay sensitivity of at least 0.005%. The estimated median hematological RFS among the 80 patients using the higher sensitivity assay was 24.2 months (95% CI: 17.9, NE).

14.2 Relapsed/Refractory B-cell Precursor ALL

TOWER Study

The efficacy of BLINCYTO was compared to standard of care (SOC) chemotherapy in a randomized, open-label, multicenter study (TOWER Study). Eligible patients were ≥ 18 years of age with relapsed or refractory B-cell precursor ALL [> 5% blasts in the bone marrow and refractory to primary induction therapy or refractory to last therapy, untreated first relapse with first remission duration < 12 months, untreated second or later relapse, or relapse at any time after allogeneic hematopoietic stem cell transplantation (alloHSCT)]. BLINCYTO was administered at 9 mcg/day on Days 1-7 and 28 mcg/day on Days 8-28 for Cycle 1, and 28 mcg/day on Days 1-28 for Cycles 2-5 in 42-day cycles and for Cycles 6-9 in 84-day cycles. Dose adjustment was possible in case of adverse events. SOC chemotherapy included fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor (FLAG);

high-dose cytarabine arabinoside (HiDAC); high-dose methotrexate- (HDMTX) based combination; or clofarabine/clofarabine-based regimens.

There were 405 patients randomized 2:1 to receive BLINCYTO or investigator-selected SOC chemotherapy. Randomization was stratified by age (< 35 years vs. ≥ 35 years of age), prior salvage therapy (yes vs. no), and prior alloHSCT (yes vs. no) as assessed at the time of consent. The demographics and baseline characteristics were well-balanced between the two arms (see Table 12).

Table 12. Demographics and Baseline Characteristics in TOWER Study

Characteristics	BLINCYTO (N = 271)	Standard of Care (SOC) Chemotherapy (N = 134)
Age		
Median, years (min, max)	37 (18, 80)	37 (18, 78)
< 35 years, n (%)	124 (46)	60 (45)
≥ 35 years, n (%)	147 (54)	74 (55)
≥ 65 years, n (%)	33 (12)	15 (11)
≥ 75 years, n (%)	10 (4)	2 (2)
Males, n (%)	162 (60)	77 (58)
Race, n (%)		
American Indian or Alaska Native	4 (2)	1 (1)
Asian	19 (7)	9 (7)
Black (or African American)	5 (2)	3 (2)
Multiple	2 (1)	0
Native Hawaiian or Other Pacific Islander	1 (0)	1 (1)
Other	12 (4)	8 (6)
White	228 (84)	112 (84)
Prior salvage therapy	171 (63)	70 (52)
Prior alloHSCT[1]	94 (35)	46 (34)
Eastern Cooperative Group Status - n (%)		
0	96 (35)	52 (39)
1	134 (49)	61 (46)
2	41 (15)	20 (15)
Unknown	0	1 (1)
Refractory to salvage treatment - n (%)		
Yes	87 (32)	34 (25)
No	182 (67)	99 (74)
Unknown	2 (1)	1 (1)
Maximum of central/local bone marrow blasts - n (%)		
≤ 5%	0	0
> 5 to < 10%	9 (3)	7 (5)
10 to < 50%	60 (22)	23 (17)
≥ 50%	201 (74)	104 (78)
Unknown	1 (0)	0

[1] alloHSCT = allogeneic hematopoietic stem cell transplantation

Of the 271 patients randomized to the BLINCYTO arm, 267 patients received BLINCYTO treatment. The median number of treatment cycles was two (range: 1 to 9 cycles); 267 (99%) received Cycles 1-2 (induction), 86 (32%) received Cycles 3-5 (consolidation), and 27 (10%) received Cycles 6-9 (continued therapy). Of the 134 patients on the SOC arm, 25 dropped out prior to start of study treatment, and 109 patients received a median of 1 treatment cycle (range: 1 to 4 cycles).

The determination of efficacy was based on overall survival (OS). The study demonstrated statistically significant improvement in OS for patients treated with BLINCYTO as compared to SOC chemotherapy.

See Figure 1 and Table 13 below for efficacy results from the TOWER Study.

Figure 1. Kaplan-Meier Curve of Overall Survival in TOWER Study

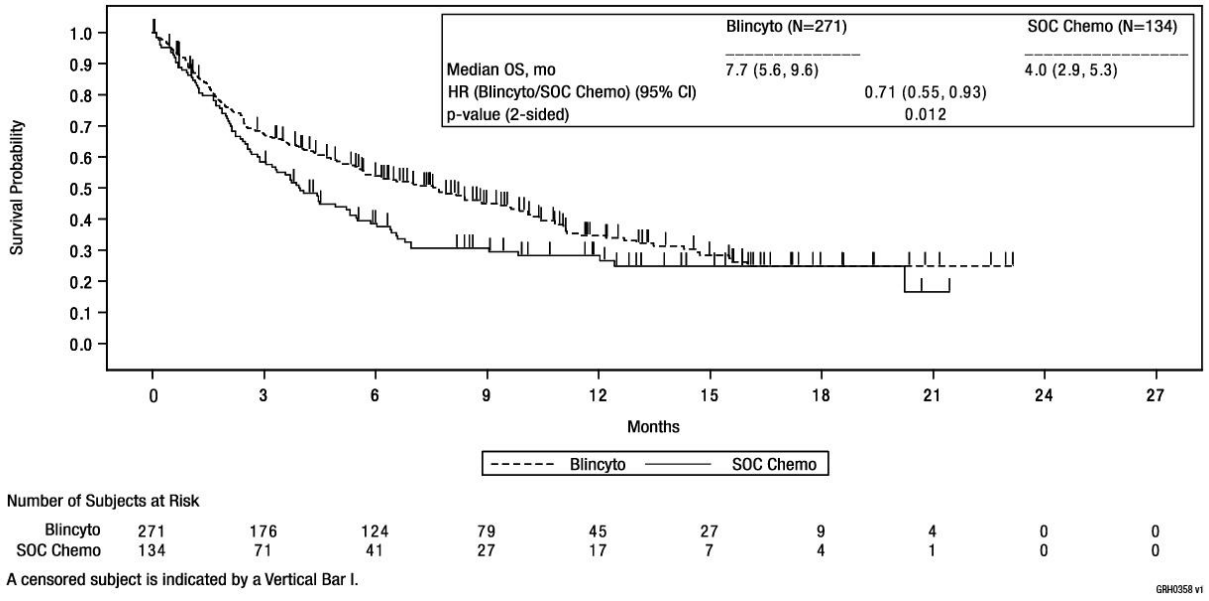

Table 13. Efficacy Results in Patients ≥ 18 Years of Age with Philadelphia Chromosome-Negative Relapsed or Refractory B-cell Precursor ALL (TOWER Study)

	BLINCYTO (N = 271)	**SOC Chemotherapy** (N = 134)
Overall Survival		
Number of deaths (%)	164 (61)	87 (65)
Median, months [95% CI]	7.7 [5.6, 9.6]	4.0 [2.9, 5.3]
Hazard Ratio [95% CI][1]	0.71 [0.55, 0.93]	
p-value[2]	0.012	
Overall Response		
CR[4]/CRh*[5], n (%) [95% CI]	115 (42) [37, 49]	27 (20) [14, 28]
Treatment difference [95% CI]	22 [13, 31]	
p-value[3]	< 0.001	
CR, n (%) [95% CI]	91 (34) [28, 40]	21 (16) [10, 23]
Treatment difference [95% CI]	18 [10, 26]	
p-value[3]	< 0.001	
MRD Response[6] for CR/CRh*		
n1/n2 (%)[7] [95% CI]	73/115 (64) [54, 72]	14/27 (52) [32, 71]

1 Based on stratified Cox's model.

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

3 The p-value was derived using Cochran-Mantel-Haenszel test.

4 CR (complete remission) 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).

5 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).

6 MRD (minimum residual disease) response was defined as MRD by PCR or flow cytometry < 1×10^{-4} (0.01%).

7 n1: number of patients who achieved MRD response and CR/CRh*; n2: number of patients who achieved CR/CRh* and had a postbaseline assessment.

Study MT103-211

Study MT103-211 was 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 alloHSCT, and had ≥ 10% blasts in bone marrow).

BLINCYTO was administered as a continuous intravenous infusion. The recommended dose for this study was determined to be was 9 mcg/day on Days 1-7 and 28 mcg/day on Days 8-28 for Cycle 1, and 28 mcg/day on Days 1-28 for subsequent cycles. Dose adjustment was possible in case of adverse events. The treated population included 185 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, the median age was 39 years (range: 18 to 79 years), 63 out of 185 (34.1%) had undergone HSCT prior to receiving BLINCYTO, and 32 out of 185 (17.3%) had received more than 2 prior salvage therapies.

Efficacy was based on the complete remission (CR) rate, duration of CR, and proportion of patients with an MRD-negative CR/CR with partial hematological recovery (CR/CRh*) within 2 cycles of treatment with BLINCYTO. Table 14 shows the efficacy results from this study. The HSCT rate among those who achieved CR/CRh* was 39% (30 out of 77).

Table 14: Efficacy Results in Patients ≥ 18 Years of Age with Philadelphia Chromosome-Negative Relapsed or Refractory B-cell Precursor ALL (Study MT103-211)

	N = 185		
	CR[1]	**CRh*[2]**	**CR/CRh***
n (%) [95% CI]	60 (32.4) [25.7, 39.7]	17 (9.2) [5.4, 14.3]	77 (41.6) [34.4, 49.1]
MRD response[3]			
n1/n2 (%)[4] [95% CI]	48/60 (80.0) [67.7, 89.2]	10/17 (58.8) [32.9, 81.6]	58/77 (75.3) [64.2, 84.4]
DOR/RFS[5]			
Median (months) (range)	6.7 (0.46 – 16.5)	5.0 (0.13 – 8.8)	5.9 (0.13 – 16.5)

[1] CR (complete remission) 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).

[2] CRh* (complete remission with partial hematological recovery) 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).

[3] MRD (minimal residual disease) response was defined as MRD by PCR < 1×10^{-4} (0.01%).

[4] n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. Six CR/CRh* responders with missing MRD data were considered as MRD-nonresponders.

[5] DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh* 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.

ALCANTARA Study

The efficacy of BLINCYTO for treatment of Philadelphia chromosome-positive B-cell precursor ALL was evaluated in an open-label, multicenter, single-arm study (ALCANTARA 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 at 9 mcg/day on Days 1-7 and 28 mcg/day on Days 8-28 for Cycle 1, and 28 mcg/day on Days 1-28 for subsequent cycles. 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). The demographics and baseline characteristics are shown in Table 15.

Table 15. Demographics and Baseline Characteristics in ALCANTARA Study

Characteristic	**BLINCYTO (N = 45)**
Age	
Median, years (min, max)	55 (23, 78)
≥ 65 years and < 75 years, n (%)	10 (22)
≥ 75 years, n (%)	2 (4)
Males, n (%)	24 (53)

Race, n (%)	
Asian	1 (2)
Black (or African American)	3 (7)
Other	2 (4)
White	39 (87)
Disease History	
Prior TKI treatment[1], n (%)	
1	7 (16)
2	21 (47)
≥ 3	17 (38)
Prior salvage therapy	31 (62)
Prior alloHSCT[2]	20 (44)
Bone marrow blasts[3]	
≥ 50% to < 75%	6 (13)
≥ 75%	28 (62)

[1] Number of patients that failed ponatinib = 23 (51%)
[2] alloHSCT = allogeneic hematopoietic stem cell transplantation
[3] centrally assessed

Efficacy was based on the complete remission (CR) rate, duration of CR, and proportion of patients with an MRD-negative CR/CR with partial hematological recovery (CR/CRh*) within 2 cycles of treatment with BLINCYTO. Table 16 shows the efficacy results from ALCANTARA Study. Five of the 16 responding (31%) patients underwent allogeneic HSCT in CR/CRh* induced with BLINCYTO. There were 10 patients with documented T315I mutation; four achieved CR within 2 cycles of treatment with BLINCYTO.

Table 16. Efficacy Results in Patients ≥ 18 Years of Age with Philadelphia Chromosome-Positive Relapsed or Refractory B-cell Precursor ALL (ALCANTARA Study)

	N = 45		
	CR[1]	**CRh*[2]**	**CR/CRh***
n (%) [95% CI]	14 (31) [18, 47]	2 (4) [1, 15]	16 (36) [22, 51]
MRD response[3]			
n1/n2 (%)[4] [95% CI]	12/14 (86) [57, 98]	2/2 (100) [16, 100]	14/16 (88) [62, 98]
DOR/RFS[5]			
Median (months) (range)	6.7 (3.6 – 12.0)	NE[6] (3.7 – 9.0)	6.7 (3.6 – 12.0)

1 CR (complete remission) 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).

2 CRh* (complete remission with partial hematological recovery) 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).

3 MRD (minimal residual disease) response was defined as MRD by PCR < 1×10^{-4}.

4 n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. Six CR/CRh* responders with missing MRD data were considered as MRD-nonresponders.

5 DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh* 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.

6 NE = not estimable

Study MT103-205

Study MT103-205 was an open-label, multicenter, single-arm study in pediatric patients with relapsed or refractory B-cell precursor ALL (second or later bone marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments, and had > 25% blasts in bone marrow). BLINCYTO was administered at 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. Dose adjustment was possible in case of adverse events. Patients who responded to BLINCYTO but later relapsed had the option to be retreated with BLINCYTO.

Among the 70 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. The median number of treatment cycles was 1 (range: 1 to 5).

Twenty-three out of 70 (32.9%) patients achieved CR/CRh* within the first 2 treatment cycles with 17 out of 23 (73.9%) occurring within cycle 1 of treatment. See Table 17 for the efficacy results from the study. The HSCT rate among those who achieved CR/CRh* was 48% (11 out of 23).

Table 17: Efficacy Results in Patients < 18 Years of Age with Relapsed or Refractory B-cell precursor ALL (Study MT103-205)

	N = 70		
	CR[1]	**CRh*[2]**	**CR/CRh***
n (%) [95% CI]	12 (17.1) [9.2, 28.0]	11 (15.7) [8.1, 26.4]	23 (32.9) [22.1, 45.1]
MRD response[3]			
n1/n2 (%)[4] [95% CI]	6/12 (50.0) [21.1, 78.9]	4/11 (36.4) [10.9, 69.2]	10/23 (43.5) [23.2, 65.5]
DOR/RFS[5]			
Median (months) (range)	6.0 (0.5 – 12.1)	3.5 (0.5 – 16.4)	6.0 (0.5 – 16.4)

1. CR (complete remission) was defined as ≤ 5% of blasts in the bone marrow, no evidence of circulating blasts or extra-medullary disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).
2. CRh* (complete remission with partial hematological recovery) was defined as ≤ 5% of blasts in the bone marrow, no evidence of circulating blasts or extramedullary disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).
3. MRD (minimal residual disease) response was defined as MRD by PCR or flow cytometry < 1×10^{-4} (0.01%).
4. n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. One CR/CRh* responder with missing MRD data was considered as a MRD-nonresponder.
5. DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh* 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each BLINCYTO package contains:

- One BLINCYTO (blinatumomab) for injection 35 mcg single-dose vial containing a sterile, preservative-free, white to off-white lyophilized powder and
- One IV Solution Stabilizer 10 mL single-dose glass vial containing a sterile, preservative-free, colorless to slightly yellow, clear solution.

Store BLINCYTO and IV Solution Stabilizer vials in the original package refrigerated at 2°C to 8°C and protect from light until time of use. Do not freeze.

BLINCYTO and IV Solution Stabilizer vials may be stored for a maximum of 8 hours at room temperature [23°C to 27°C] in the original carton to protect from light.

Refer to the expiry date printed on the outer carton.

17 PATIENT COUNSELING INFORMATION

Cytokine Release Syndrome (CRS)
Advise patients of the risk of CRS and infusion reactions, and to contact their healthcare professional for signs and symptoms associated with CRS or infusion reactions (pyrexia, fatigue, nausea, vomiting, chills, hypotension, rash, and wheezing) *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

Neurological Toxicities
Advise patients of the risk of neurological toxicities, and to contact their healthcare professional for signs and symptoms associated with this event (convulsions, speech disorders, and confusion) *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Infections
Advise patients of the risk of infections, and to contact their healthcare professional for signs or symptoms of infection *[see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]*.

Inform patients of the importance of keeping the skin clean around the intravenous catheter to reduce the risk of infection.

Pancreatitis
Advise patients of the risk of pancreatitis and to contact their healthcare provider for signs or symptoms of pancreatitis which include severe and persistent stomach pain, with or without nausea and vomiting *[see Warnings and Precautions (5.8) and Adverse Reactions (6.3)]*.

Driving and Engaging in Hazardous Occupations
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. Patients should be advised that they may experience neurological events *[see Warnings and Precautions (5.6)]*.

Infusion Pump Errors
Inform patients they should not adjust the setting on the infusion pump. Any changes to pump function may result in dosing errors. If there is a problem with the infusion pump or the pump alarms, patients should contact their doctor or nurse immediately.

BLINCYTO® (blinatumomab)

Product Owner:
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One Amgen Center Drive,
Thousand Oaks,
CA91320 – 1799, USA

Date of Revision: August 2022

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