HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BLINCYTO® safely and effectively. See full prescribing information for BLINCYTO.

BLINCYTO® (blinatumomab) for injection, for intravenous use
Initial U.S. Approval: 2014

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES
See full prescribing information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.3, 5.1)**
- **Neurological toxicities, which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.3, 5.2)**

----------RECENT MAJOR CHANGES----------

• Indications and Usage (1)	8/2016
• Dose and Administration (2.1, 2.2, 2.3, 2.4, 2.5)	8/2016
• Warnings and Precautions (5.1, 5.2, 5.7, 5.8, 5.11)	8/2016

----------INDICATIONS AND USAGE----------

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit in subsequent trials. (1)

----------DOSAGE AND ADMINISTRATION----------

- Dosage
  - A single cycle of treatment consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days). (2.1)
  - For patients greater than or equal to 45 kg, in Cycle 1, administer BLINCYTO at 9 mcg/day on Days 1-7 and at 28 mcg/day on Days 8-28. For subsequent cycles, administer BLINCYTO at 28 mcg/day on Days 1-28. (2.1)
  - For patients less than 45 kg, in Cycle 1, administer BLINCYTO at 5 mcg/m^2/day on Days 1-7 and at 15 mcg/m^2/day on Days 8-28. For subsequent cycles, administer BLINCYTO at 15 mcg/m^2/day on Days 1-28. (2.1)
- Administration
  - Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. (2.2)
  - Premedicate with dexamethasone. (2.2)
  - Administer as a continuous intravenous infusion at a constant flow rate using an infusion pump. (2.2)
- Use dose adjustments for toxicity (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 35 mcg of lyophilized powder in a single-dose vial for reconstitution. (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to blinatumomab or to any component of the product formulation. (4)

----------WARNINGS AND PRECAUTIONS----------

- Infections: Monitor patients for signs or symptoms; treat appropriately. (5.3)
- Effects on Ability to Drive and Use Machines: 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. (5.6)
- Pancreatitis: Evaluate patients who develop signs and symptoms of pancreatitis. Management of pancreatitis may require either temporary interruption or discontinuation of BLINCYTO. (5.8)
- Preparation and Administration Errors: Strictly follow instructions for preparation (including admixing) and administration. (5.10)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (≥ 20%) were pyrexia, headache, nausea, edema, hypokalemia, anemia, febrile neutropenia, neutropenia, thrombocytopenia, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. *[see Dosage and Administration (2.3), Warnings and Precautions (5.1)]*.**
- **Neurological toxicities, which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. *[see Dosage and Administration (2.3), Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

BLINCYTO is indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) *[see Dosage and Administration (2.1)]*.

This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit in subsequent trials *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

- A single cycle of treatment of BLINCYTO consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days).
- A treatment course consists of up to 2 cycles of BLINCYTO for induction followed by 3 additional cycles for consolidation treatment (up to a total of 5 cycles).
- See Table 1 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 1. BLINCYTO Recommended Dosage

Patient Weight	**Cycle 1***			**Subsequent Cycles***	
	Days 1-7	**Days 8-28**	**Days 29-42**	**Days 1-28**	**Days 29-42**
Greater than or equal to 45 kg *(fixed-dose)*	9 mcg/day	28 mcg/day	14-day treatment-free interval	28 mcg/day	14-day treatment-free interval
Less than 45 kg *(BSA-based dose)*	5 mcg/m^2/day *(not to exceed 9 mcg/day)*	15 mcg/m^2/day *(not to exceed 28 mcg/day)*		15 mcg/m^2/day *(not to exceed 28 mcg/day)*	

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

2.2 Administration

- 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 (eg, 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 dexamethasone 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 5 mg/m^2 of dexamethasone, to a maximum dose of 20 mg prior to the first dose of BLINCYTO in the first 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 in the first cycle.
- 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.
- Prepared BLINCYTO infusion bags *[see Dosage and Administration (2.4)]* should be infused over 24 hours or 48 hours. The choice between 24 hours or 48 hours of the infusion duration should be made by the treating physician considering the frequency of the infusion bag changes.
- The starting volume (270 mL) is more than the volume administered to the patient (240 mL) to account for the priming of the IV tubing and to ensure that the patient will receive the full dose of BLINCYTO.
- Infuse BLINCYTO 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/h for a duration of 24 hours, OR
    - Infusion rate of 5 mL/h for a duration of 48 hours
- The BLINCYTO solution must be administered using IV 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, BLINCYTO should be infused through a dedicated lumen.**
- At the end of the infusion, any unused BLINCYTO solution in the IV bag and IV tubing should be disposed of in accordance with local requirements.

2.3 Dosage Adjustments

If the interruption after an adverse event 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 event is longer than 7 days, start a new cycle.

Toxicity	Grade*	Patients Greater Than or Equal to 45 kg	Patients Less Than 45 kg
Cytokine Release Syndrome (CRS)	Grade 3	Withhold BLINCYTO until resolved, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.	Withhold BLINCYTO until resolved, 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.
	Grade 4	Discontinue BLINCYTO permanently.	
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 toxicity does not recur. If the toxicity occurred at 9 mcg/day, or if the toxicity 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 toxicity does not recur. 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	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 toxicity does not recur. If the toxicity 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 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.

2.4 Reconstitution and Preparation of Solution for Infusion

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 (5.10)]*.

Call 1-800-77-AMGEN (1-800-772-6436) if you have questions about the reconstitution and preparation of BLINCYTO.

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 Gather Supplies

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

- IV Solution Stabilizer is provided with the BLINCYTO package and is used to coat the IV bag prior to addition of reconstituted BLINCYTO to prevent adhesion of BLINCYTO to IV bags and IV tubing.

Before preparation, ensure you have the following supplies ready:

- 1 or 2 package(s) of BLINCYTO as needed for each dosage.
  - Patients weighing greater than or equal to 45 kg: 2 packages of BLINCYTO are needed for preparation of 28 mcg/day dose infused over 48 hours at a rate of 5 mL/h
  - Patients weighing less than 45 kg: 2 packages of BLINCYTO are needed for preparation of 15 mcg/m^2/day dose infused over 48 hours at a rate of 5 mL/hour for patients with a BSA greater than 1.09 m^2

The following supplies are also required, but **not** included in the package:

- Supplies to make a 270 mL 0.9% Sodium Chloride IV bag
  - An empty IV bag. Use only PVC di-ethylhexylphthalate-free (DEHP-free), polyolefin, or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
  - 0.9% Sodium Chloride Injection , USP (eg, 1000 mL)
- Preservative-free Sterile Water for Injection, USP
- Sterile, single-use disposable syringes
- 21-to 23- gauge needle(s) (recommended)
- PVC DEHP-free, polyolefin, or EVA IV tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter
  - Ensure that the IV tubing is compatible with the infusion pump.

2.4.3 Reconstitution of BLINCYTO

1. Add 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 (resulting in a final BLINCYTO concentration of 12.5 mcg/mL).
    - **Do <u>not</u> reconstitute BLINCYTO with IV Solution Stabilizer.**
2. Gently swirl contents to avoid excess foaming. **Do <u>not</u> shake.**
3. 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 <u>not</u> use if solution is cloudy or has precipitated.**

2.4.4 Preparation of BLINCYTO Infusion Bag

Verify the prescribed dose and infusion duration for each BLINCYTO infusion bag. To minimize errors, **use the specific volumes described in Tables 2 to 4 to prepare the BLINCYTO infusion bag.**

- Table 2 for patients weighing greater than or equal to 45 kg
- Tables 3 and 4 for patients weighing less than 45 kg

1. **Aseptically add 270 mL 0.9% Sodium Chloride Injection, USP to the IV bag** prior to the addition of IV Solution Stabilizer and reconstituted BLINCYTO.
    - Use only PVC DEHP-free, polyolefin, or EVA IV bags/pump cassettes
2. **Aseptically transfer 5.5 mL IV Solution Stabilizer to the IV 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 reconstituted BLINCYTO** into the IV bag containing 0.9% Sodium Chloride Injection, USP and IV Solution Stabilizer. Gently mix the contents of the bag to avoid foaming.
    - Refer to Tables 2 to 4 for the specific volume of reconstituted BLINCYTO
4. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
    - Use only PVC DEHP-free, polyolefin, or EVA IV tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter
    - Ensure that the IV tubing is compatible with the infusion pump
5. Remove air from the IV bag. This is particularly important for use with an ambulatory infusion pump. **<u>Prime the IV tubing only with the prepared solution for infusion</u>**. **Do not prime with 0.9% Sodium Chloride Injection, USP.**
6. Store at 2°C to 8°C if not used immediately *[see Dosage and Administration (2.5)]*.

Table 2. For Patients Weighing Greater Than or Equal to 45 kg: Volumes of 0.9% Sodium Chloride Injection, USP, IV Solution Stabilizer, and Reconstituted BLINCYTO to add to IV Bag

0.9% Sodium Chloride Injection, USP (starting volume)			270 mL
IV Solution Stabilizer			5.5 mL
Dose	**Infusion Duration**	**Infusion Rate**	**Reconstituted BLINCYTO**
9 mcg/day	24 hours	10 mL/hour	0.83 mL
	48 hours	5 mL/hour	1.7 mL
28 mcg/day	24 hours	10 mL/hour	2.6 mL
	48 hours	5 mL/hour	5.2 mL*

* 2 packages of BLINCYTO are needed for preparation of 28 mcg/day dose infused over 48 hours at a rate of 5 mL/hour.

Table 3. For Patients Weighing Less Than 45 kg: Volumes of 0.9% Sodium Chloride Injection, USP, IV Solution Stabilizer, and Reconstituted BLINCYTO to add to IV Bag for 5 mcg/m^2/day Dose

0.9% Sodium Chloride Injection, USP (starting volume)				270 mL
IV Solution Stabilizer				5.5 mL
Dose	**Infusion Duration**	**Infusion Rate**	**BSA (m^2)**	**Reconstituted BLINCYTO**
5 mcg/m^2/day	24 hours	10 mL/hour	1.5 – 1.59	0.7 mL
			1.4 – 1.49	0.66 mL
			1.3 – 1.39	0.61 mL
			1.2 – 1.29	0.56 mL
			1.1 – 1.19	0.52 mL
			1– 1.09	0.47 mL
			0.9 – 0.99	0.43 mL
			0.8 – 0.89	0.38 mL
			0.7 – 0.79	0.33 mL
			0.6 – 0.69	0.29 mL
			0.5 – 0.59	0.24 mL
			0.4 – 0.49	0.2 mL
	48 hours	5 mL/hour	1.5 – 1.59	1.4 mL
			1.4 – 1.49	1.3 mL
			1.3 – 1.39	1.2 mL
			1.2 – 1.29	1.1 mL
			1.1 – 1.19	1 mL
			1– 1.09	0.94 mL
			0.9 – 0.99	0.85 mL
			0.8 – 0.89	0.76 mL
			0.7 – 0.79	0.67 mL
			0.6 – 0.69	0.57 mL
			0.5 – 0.59	0.48 mL
			0.4 – 0.49	0.39 mL

Table 4. For Patients Weighing Less Than 45 kg: Volumes of 0.9% Sodium Chloride Injection, USP, IV Solution Stabilizer, and Reconstituted BLINCYTO to add to IV Bag for 15 mcg/m^2/day Dose

0.9% Sodium Chloride Injection, USP (starting volume)				270 mL
IV Solution Stabilizer				5.5 mL
Dose	**Infusion Duration**	**Infusion Rate**	**BSA (m^2)**	**Reconstituted BLINCYTO**
15 mcg/m^2/day	24 hours	10 mL/hour	1.5 – 1.59	2.1 mL
			1.4 – 1.49	2 mL
			1.3 – 1.39	1.8 mL
			1.2 – 1.29	1.7 mL
			1.1 – 1.19	1.6 mL
			1– 1.09	1.4 mL
			0.9 – 0.99	1.3 mL
			0.8 – 0.89	1.1 mL
			0.7 – 0.79	1 mL
			0.6 – 0.69	0.86 mL
			0.5 – 0.59	0.72 mL
			0.4 – 0.49	0.59 mL
	48 hours	5 mL/hour	1.5 – 1.59	4.2 mL*
			1.4 – 1.49	3.9 mL*
			1.3 – 1.39	3.7 mL*
			1.2 – 1.29	3.4 mL*
			1.1 – 1.19	3.1 mL*
			1– 1.09	2.8 mL
			0.9 – 0.99	2.6 mL
			0.8 – 0.89	2.3 mL
			0.7 – 0.79	2 mL
			0.6 – 0.69	1.7 mL
			0.5 – 0.59	1.4 mL
			0.4 – 0.49	1.2 mL

*2 packages of BLINCYTO are needed for preparation of 15 mcg/ m^2/day dose infused over 48 hours at a rate of 5 mL/hour for patients with a BSA greater than 1.09 m^2.

2.5 Storage Requirements

The information in Table 5 indicates the storage time for the reconstituted BLINCYTO vial and prepared infusion bag.

Store lyophilized BLINCYTO and IV Solution Stabilizer vials for a maximum of 8 hours at room temperature in the original carton to protect from light *[see How Supplied/Storage and Handling (16.2)]*.

Table 5. Storage Time for Reconstituted BLINCYTO Vial and Prepared BLINCYTO Infusion Bag

Maximum Storage Time of Reconstituted BLINCYTO Vial		Maximum Storage Time of Prepared BLINCYTO Infusion Bag	
Room Temperature 23°C to 27°C (73°F to 81°F)	Refrigerated 2°C to 8°C (36°F to 46°F)	Room Temperature 23°C to 27°C (73°F to 81°F)	Refrigerated 2°C to 8°C (36°F to 46°F)
4 hours	24 hours	48 hours*	8 days

* Storage time includes infusion time. If IV bag containing BLINCYTO solution for infusion 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 injection: 35 mcg of 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.

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

Serious adverse events that may be associated with CRS included pyrexia, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, and increased total bilirubin; these events infrequently led to BLINCYTO discontinuation. Life-threatening or fatal CRS was reported in patients receiving BLINCYTO. In some cases, disseminated intravascular coagulation (DIC), capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) have been reported in the setting of CRS.

Patients should be closely monitored for signs or symptoms of these events. Management of these events may require either temporary interruption or discontinuation of BLINCYTO *[see Dosage and Administration (2.3)]*.

5.2 Neurological Toxicities

In patients receiving BLINCYTO in clinical trials, neurological toxicities have occurred in approximately 64% of patients. The median time to onset of any neurological toxicity was 4 days. The most common (≥ 10%) manifestations of neurological toxicity were headache, tremor, dizziness, and altered state of

consciousness; 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 17% of patients and included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. The majority of events resolved following interruption of BLINCYTO, but some resulted in treatment discontinuation.

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.

Monitor patients receiving BLINCYTO for signs and symptoms of neurological toxicities, and interrupt or discontinue BLINCYTO as recommended *[see Dosage and Administration (2.3)]*.

5.3 Infections

In patients receiving BLINCYTO in clinical trials, 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. As appropriate, administer prophylactic antibiotics and employ surveillance testing during treatment with BLINCYTO. Monitor patients for signs and symptoms of infection and treat appropriately.

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), which may be life-threatening or fatal, has been observed in patients receiving BLINCYTO. 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)]*.

5.5 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. 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. In clinical trials, the median time to onset of elevated liver enzymes was 3 days.

In patients receiving BLINCYTO, although the majority of these events were observed in the setting of CRS, some were observed outside of this setting. For these events, the median time to onset was 15 days. Grade 3 or greater elevations in liver enzymes occurred in approximately 6% 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 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 trials and the post-marketing setting.

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.

5.10 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)]*.

5.11 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 adverse reactions are discussed in greater detail in other sections of the label:

- 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.

The safety data described in this section reflect exposure to BLINCYTO in clinical trials in which 282 patients (212 adult and 70 pediatric patients) with relapsed or refractory ALL were treated with a recommended dose and schedule. All patients received at least one dose of BLINCYTO. The most common adverse reactions (≥ 20%) in the safety population were pyrexia, headache, nausea, edema, hypokalemia, anemia, febrile neutropenia, neutropenia, thrombocytopenia, and abdominal pain. For some adverse reactions, there were differences in incidence rates by age subgroup *[see Use in Special Populations (8.4, 8.5)]*.

The safety population included 225 patients weighing 45 kg or more and 57 patients weighing less than 45 kg. In general, the adverse reactions in the BLINCYTO-treated patients less than 45 kg were similar in type to those seen in patients greater than or equal to 45 kg.

Patients Greater Than or Equal to 45 kg

The median age of patients greater than or equal to 45 kg was 34 years (range: 11 to 79 years), 63% were male, 79% were White, 3% were Asian, and 3% were Black or African American.

Serious adverse reactions were reported in 61% of patients. The most common serious adverse reactions (≥ 2%) included febrile neutropenia, pyrexia, sepsis, pneumonia, device-related infection, neutropenia, tremor, overdose, encephalopathy, infection, confusion, and headache. Adverse reactions of grade 3 or higher were reported in 80% of patients. Discontinuation of therapy due to adverse reactions occurred in 16% of patients treated with BLINCYTO. The adverse reactions reported most frequently as the reason for discontinuation of treatment included encephalopathy and sepsis. Fatal adverse events occurred in 12% of patients. The majority of the fatal events were infections. No fatal adverse events occurred on treatment among patients in remission.

Patients Less Than 45 kg

The median age of patients less than 45 kg was 6 years (range: 7 months to 64 years), 68% were male, and 77% were White.

Serious adverse reactions were reported in 51% patients. The most common serious adverse reactions (≥ 2%) included pyrexia, febrile neutropenia, cytokine release syndrome, convulsion, device-related infection, hypoxia, sepsis, and overdose. Adverse reactions of Grade 3 or higher were reported in 88% of patients. Discontinuation of therapy due to adverse reactions occurred in 5% of patients treated with BLINCYTO. Adverse reactions that led to discontinuation of treatment were CRS and fungal infection.

Three patients experienced a fatal adverse event within 30 days of the last dose of BLINCYTO (2 infection and 1 multi-organ failure after undergoing subsequent HSCT).

The adverse reactions with ≥ 10% incidence for any grade or ≥ 5% incidence for Grade 3 or higher are summarized in Table 6.

Table 6. Adverse Reactions With ≥ 10% Incidence for Any Grade or ≥ 5% Incidence for Grade 3 or Higher

Adverse Reaction	Patients Greater Than or Equal to 45 kg (N = 225)		Patients Less Than 45 kg (N = 57)	
	Any Grade[1] (%)	Grade 3 or Higher[1] (%)	Any Grade[1] (%)	Grade 3 or Higher[1] (%)
Blood and lymphatic system disorders				
Febrile neutropenia	25	23	19	18
Anemia[2]	21	16	42	35
Neutropenia[3]	19	18	32	32
Thrombocytopenia[4]	16	12	35	35
Leukopenia[5]	14	12	26	21
Cardiac disorders				
Arrhythmia[6]	19	2	11	0
Gastrointestinal disorders				
Nausea	26	0	30	0
Constipation	20	0	9	2
Diarrhea[7]	19	1	19	4
Abdominal pain[8]	19	2	23	4
Vomiting	13	0	26	2
General disorders and administration site conditions				
Pyrexia	64	7	75	16
Edema[9]	30	2	11	0
Fatigue	16	1	9	0
Chills	15	0	2	0
Chest pain	10	1	4	0
Immune system disorders				
Infusion-related reactions[10]	34	4	44	12
Cytokine release syndrome[11]	13	3	11	4
Infections and infestations				
Infections – pathogen unspecified[12]	45	27	42	21
Bacterial infections[12]	19	12	11	5

Fungal infections[12]	14	7	7	5
Viral infections[12]	13	4	9	2
Investigations				
Decreased immunoglobulins[13]	12	2	5	0
Increased weight	11	0	18	5
Metabolism and nutrition disorders				
Hypokalemia[14]	27	8	21	16
Hypomagnesemia[15]	12	0	9	0
Hyperglycemia[16]	12	7	11	4
Decreased appetite	10	3	4	0
Hypophosphatemia	6	4	16	5
Hypocalcemia	5	2	11	4
Musculoskeletal and connective tissue disorders				
Back pain	15	2	16	4
Pain in extremity	12	1	11	4
Bone pain	11	3	9	0
Arthralgia	10	2	4	0
Nervous system disorders				
Headache	36	4	28	2
Tremor[17]	19	1	7	0
Dizziness	13	< 1	5	0
Altered state of consciousness[18]	10	1	7	4
Psychiatric disorders				
Insomnia	14	0	5	0
Respiratory, thoracic, and mediastinal disorders				
Cough	20	< 1	18	0
Dyspnea[19]	15	5	4	4
Epistaxis	10	< 1	9	2
Skin and subcutaneous tissue disorders				
Rash[20]	21	2	11	0
Vascular disorders				
Hypotension[21]	13	3	12	2
Hypertension	9	5	25	5

[1] Grading is based on the Common Terminology Criteria for Adverse Events (CTCAE). Grade 3 is severe, Grade 4 is life-threatening, and Grade 5 is fatal.
[2] Anemia includes anemia and hemoglobin decreased.
[3] Neutropenia includes neutropenia and neutrophil count decreased.
[4] Thrombocytopenia includes thrombocytopenia and platelet count decreased.
[5] Leukopenia includes leukopenia and white blood cell count decreased.
[6] Arrhythmia includes tachycardia, sinus tachycardia, bradycardia, sinus bradycardia, supraventricular tachycardia, atrial fibrillation, ventricular fibrillation, atrial tachycardia, and ventricular extrasystoles.
[7] Diarrhea includes diarrhea, colitis, enteritis, gastroenteritis, and neutropenic colitis.
[8] Abdominal pain includes abdominal pain, abdominal pain upper, gastrointestinal pain, and abdominal pain lower.
[9] Edema includes peripheral edema, edema, and generalized edema.
[10] Infusion-related reactions is a composite term that includes infusion related reaction and the following events occurring within the first 48 hours of infusion: pyrexia, hypotension, cytokine release syndrome, hypertension, myalgia, maculo-papular rash, rash, face swelling, and tachypnea.
[11] Cytokine release syndrome includes cytokine release syndrome, capillary leak syndrome, cytokine storm, and infusion-related reaction.
[12] Higher level group term.
[13] Decreased immunoglobulins includes immunoglobulins decreased, blood immunoglobulin G decreased, blood immunoglobulin A decreased, blood immunoglobulin M decreased, and hypogammaglobulinaemia.
[14] Hypokalemia includes hypokalemia and blood potassium decreased.
[15] Hypomagnesemia includes hypomagnesemia and blood magnesium decreased.
[16] Hyperglycemia includes hyperglycemia and blood glucose increased.
[17] Tremor includes tremor and resting tremor.
[18] Altered state of consciousness includes somnolence, mental status changes, lethargy, depressed level of consciousness, altered state of consciousness, stupor, and disturbance in attention.
[19] Dyspnea includes dyspnea, respiratory failure, wheezing, dyspnea exertional, bronchospasm, acute respiratory failure, bronchial hyperreactivity, and respiratory distress.
[20] Rash includes rash, erythema, maculo-papular rash, generalized rash, macular rash, papular rash, dermatitis diaper, erythematous rash, and vesicular rash.
[21] Hypotension includes hypotension, circulatory collapse, and hypovolemic shock.

For patients weighing greater than or equal to 45 kg and patients less than 45 kg, additional important adverse reactions that did not meet the threshold criteria for inclusion in Table 6 were, in each weight cohort respectively: leukocytosis (2%, 4%), lymphopenia (1%, 2%), increased gamma-glutamyl-transferase (6%, 2%), tumor lysis syndrome (4%, 0%), hypoalbuminemia (4%, 7%), encephalopathy (5%, 2%), paresthesia (5%, 2%), aphasia (4%, 0%), convulsion (2%, 4%), memory impairment (2%, 0%), cognitive disorder (1%, 0%), speech disorder (< 1%, 0%), confusional state (7%, 0%), and disorientation (3%, 0%), respectively.

Hypersensitivity reactions related to BLINCYTO treatment were hypersensitivity (1%) and bronchospasm (< 1%).

Selected laboratory abnormalities worsening from baseline Grade 0-2 to treatment-related maximal Grade 3-4 are shown in Table 7.

Table 7. Selected Laboratory Abnormalities Worsening from Baseline Grade 0-2 to Treatment-Related Maximal Grade 3-4[1]

	Patients Greater Than or Equal to 45 kg Grade 3 or 4 (%)	**Patients Less Than 45 kg** Grade 3 or 4 (%)
Hematology		
Decreased lymphocyte count	90	88
Decreased white blood cell count	63	79
Decreased hemoglobin	38	64

Decreased neutrophil count	67	97
Decreased platelet count	57	74
Chemistry		
Increased ALT	21	36
Increased bilirubin	13	5
Increased AST	11	18
Decreased potassium	9	30
Decreased calcium	8	4
Decreased albumin	2	2

[1] Includes only patients who had both baseline and at least one laboratory measurement during the study available.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval 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 *[see Warnings and Precautions (5.8)]*.

6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. 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 1% of patients treated with BLINCYTO tested positive for binding anti-blinatumomab antibodies. All patients who tested positive for binding antibodies also tested positive for neutralizing anti-blinatumomab antibodies. Anti-blinatumomab antibody formation may affect pharmacokinetics of BLINCYTO.

If formation of anti-blinatumomab antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) 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.

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 (eg, warfarin) or drug concentrations (eg, 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 use 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. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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 (5.11)]*.

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 nursing infants from BLINCYTO, including B-cell lymphocytopenia, advise patients not to breastfeed during and for at least 48 hours after treatment with BLINCYTO.

8.3 Females and Males of Reproductive Potential

Based on its mechanism of action, 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 and for at least 48 hours after the last dose of BLINCYTO.

8.4 Pediatric Use

The safety and efficacy of BLINCYTO have been established in pediatric patients. 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.

In general, the adverse reactions in BLINCYTO-treated pediatric patients were similar in type to those seen in adult patients *[see Adverse Reactions (6.1)]*. Adverse reactions that were observed more frequently (≥ 10%) in the pediatric population compared to the adult population were anemia (41% vs 18%), thrombocytopenia (21% vs.11%), vomiting (24% vs. 13%), pyrexia (80% vs. 62%), and hypertension (26% vs. 8%). 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 (23%).

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 relapsed or refractory ALL in clinical studies of BLINCYTO, treated at the recommended dose and schedule, approximately 10% were 65 and over, while 1% 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 neurological toxicities, including cognitive disorder, encephalopathy, confusion, and serious infections *[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 the Phase 1/2 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 therapeutic dose and included fever, tremors, and headache. In the event of overdose, interrupt the infusion, monitor the patient for signs of toxicity, and provide supportive care *[see Warnings and Precautions (5.10)]*. Consider re-initiation of BLINCYTO at the correct therapeutic dose when all toxicities have resolved and no earlier than 12 hours after interruption of the infusion *[see Dosage and Administration (2.1)]*.

11 DESCRIPTION

BLINCYTO (blinatumomab) is a bispecific CD19-directed CD3 T-cell engager that binds to CD19 (expressed on cells of B-lineage origin) and CD3 (expressed on T cells). BLINCYTO 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 is supplied in a single-dose vial as a sterile, preservative-free, white to off-white lyophilized powder for intravenous administration. 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 majority 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 (C_{ss}) was achieved within a day and remained stable over time. The increase in mean C_{ss} 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/refractory ALL, the mean (SD) C_{ss} was 211 (258) pg/mL and 621 (502) pg/mL, respectively.

Distribution
The estimated mean (SD) volume of distribution based on terminal phase (Vz) was 4.52 (2.89) 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 2.92 (2.83) L/hour. The mean (SD) half-life was 2.11 (1.42) 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 (0.37 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 95.6%), 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, the mean (SD) steady state concentration (C_{ss}) values were 162 (179) and 533 (392) pg/mL at 5 and 15 mcg/m^2/day doses, respectively. The estimated mean (SD) volume of distribution (V_z), clearance (CL) and terminal half-life ($t_{1/2,z}$) were 3.91 (3.36) L/m^2, 1.88 (1.90) L/hr/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 Relapsed/Refractory Acute Lymphoblastic Leukemia

Study 1

Study 1 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 allogeneic hematopoietic stem cell transplantation [HSCT], 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 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. Seventy-seven out of 185 (41.6%) evaluable patients achieved CR/CRh* within the first 2 treatment cycles, with the majority of responses (81%, 62 out of 77) occurring within Cycle 1 of treatment. See Table 8 for efficacy results from this study. The HSCT rate among those who achieved CR/CRh* was 39% (30 out of 77).

Table 8. Study 1: Efficacy Results in Patients ≥ 18 Years of Age With Philadelphia Chromosome-Negative Relapsed or Refractory B-cell precursor Acute Lymphoblastic Leukemia (ALL)

	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}.

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.

Study 2

Study 2 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 9 for the efficacy results from the study. The HSCT rate among those who achieved CR/CRh* was 48% (11 out of 23).

Table 9. Study 2: Efficacy Results in Patients < 18 Years of Age With Relapsed or Refractory B-cell precursor Acute Lymphoblastic Leukemia (ALL)

	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 extra-medullary 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}.
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

16.1 How Supplied

Each BLINCYTO package (NDC 55513-160-01) contains:

- One BLINCYTO 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. **Do <u>not</u> use the IV Solution Stabilizer to reconstitute BLINCYTO.**

16.2 Storage and Handling

Store BLINCYTO and IV Solution Stabilizer vials in the original package refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light until time of use. Do not freeze.

Store and transport the prepared IV bag containing BLINCYTO solution for infusion at 2°C to 8°C (36°F to 46°F) conditions. Ship in packaging that has been validated to maintain temperature of the contents at 2°C to 8°C (36°F to 46°F). Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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) to a healthcare professional *[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) to a healthcare professional *[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 (6.2)]*.

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)]*.

Reduce Risk of 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)

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
U.S. License No. 1080

Patent: http://pat.amgen.com/blincyto/

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Medication Guide
BLINCYTO® (blin sye' toe)
(blinatumomab)
for injection

What is the most important information I should know about BLINCYTO?

Call your healthcare provider or get emergency medical help right away if you get any of the symptoms listed below.

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

- **Cytokine Release Syndrome (CRS) and Infusion Reactions.** Symptoms of CRS and infusion reactions may include:
  - fever
  - tiredness or weakness
  - dizziness
  - headache
  - low blood pressure
  - nausea
  - vomiting
  - chills
  - face swelling
  - wheezing or trouble breathing
  - skin rash
- **Neurologic problems.** Symptoms of neurologic problems may include:
  - seizures
  - difficulty in speaking or slurred speech
  - loss of consciousness
  - confusion and disorientation
  - loss of balance

Your healthcare provider will check for these problems during treatment with BLINCYTO. Your healthcare provider may temporarily stop or completely stop your treatment with BLINCYTO, if you have severe side effects.

See **"What are the possible side effects of BLINCYTO?"** below for other side effects of BLINCYTO.

What is BLINCYTO?

BLINCYTO is a prescription medicine used to treat a certain type of acute lymphoblastic leukemia (ALL). ALL is a cancer of the blood in which a particular kind of white blood cell is growing out of control**.**

Who should not receive BLINCYTO?

Do not receive BLINCYTO if you are allergic to blinatumomab or to any of the ingredients of BLINCYTO. See the end of this Medication Guide for a complete list of ingredients in BLINCYTO.

What should I tell my healthcare provider before receiving BLINCYTO?

Before receiving BLINCYTO, tell your healthcare provider about all of your medical conditions, including if you or your child:

- have a history of neurological problems, such as seizures, confusion, trouble speaking or loss of balance
- have an infection
- have ever had an infusion reaction after receiving BLINCYTO or other medications
- have a history of radiation treatment to the brain, or chemotherapy treatment
- are scheduled to receive a vaccine. You should not receive a "live vaccine" within 2 weeks before you start treatment with BLINCYTO, during treatment, and until your immune system recovers after you receive your last cycle of BLINCYTO. If you are not sure about the type of vaccine, ask your healthcare provider.
- are pregnant or plan to become pregnant. BLINCYTO may harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with BLINCYTO.
  - If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start treatment with BLINCYTO.
  - Females who are able to become pregnant should use an effective form of birth control during treatment with BLINCYTO, and for at least 48 hours after the last dose of BLINCYTO.
- are breastfeeding or plan to breastfeed. It is not known if BLINCYTO passes into your breast milk. You should not breastfeed during treatment with BLINCYTO and for at least 48 hours after your last treatment.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive BLINCYTO?

- BLINCYTO will be given to you by intravenous (IV) infusion into your vein by an infusion pump.
- You will receive BLINCYTO by continuous IV infusion for 4 weeks (28 days), followed by a 2 week (14 days) break during which you will not receive BLINCYTO. This is one treatment cycle (42 days). After the 2 week break, your healthcare provider will decide if you will be given additional treatment cycles of BLINCYTO.
- Your healthcare provider may 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.

- Your healthcare provider may change your dose of BLINCYTO, delay, or completely stop treatment with BLINCYTO if you have certain side effects.
- Your healthcare provider will do blood tests during treatment with BLINCYTO to check you for side effects.
- Before you receive BLINCYTO, you will be given a corticosteroid medicine to help reduce infusion reactions.
- It is very important to keep the area around the IV catheter clean to reduce the risk of getting an infection. Your healthcare provider 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 provider or nurse right away if you have any problems with your pump or your pump alarm sounds.**

What should I avoid while receiving 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.

What are the possible side effects of BLINCYTO?

BLINCYTO may cause serious side effects, including:

See **"What is the most important information I should know about BLINCYTO?"**

- **Infections.** BLINCYTO may cause life-threatening infections that may lead to death. Tell your healthcare provider right away if you develop any signs or symptoms of an infection.
- **Low white blood cell counts (neutropenia).** Neutropenia is common with BLINCYTO treatment and may sometimes be life-threatening. Low white blood cell counts can increase your risk of infection. Your healthcare provider will do blood tests to check your white blood cell count during treatment with BLINCYTO. Tell your healthcare provider right away if you get a fever.
- **Abnormal liver blood tests.** Your healthcare provider will do blood tests to check your liver before you start BLINCYTO and during treatment with BLINCYTO.
- **Inflammation of the pancreas (pancreatitis).** Pancreatitis may happen in patients treated with BLINCYTO and corticosteroids. It may be severe and lead to death. Tell your healthcare provider right away if you have severe stomach-area pain that does not go away. The pain may happen with or without nausea and vomiting.

The most common side effects of BLINCYTO include:

- fever
- headache
- nausea
- swelling of your hands, ankles, or feet
- low blood potassium (hypokalemia)
- low red blood cell count (anemia)
- low platelet count (thrombocytopenia)
- stomach pain

These are not all the possible side of effects of BLINCYTO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BLINCYTO?

Intravenous (IV) bags containing BLINCYTO for infusion will arrive in a special package.

- Do not open the package.
- Do not freeze the package.
- The package containing BLINCYTO will be opened by your healthcare provider and stored in the refrigerator at 36°F to 46°F (2°C to 8°C) for up to 8 days.
- Do not throw away (dispose of) any BLINCYTO in your household trash. Talk with your healthcare provider about disposal of BLINCYTO and used supplies.
- **Keep BLINCYTO and all medicines out of reach of children.**

General information about BLINCYTO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BLINCYTO for a condition for which it was not prescribed. Do not give BLINCYTO to other people even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about BLINCYTO that is written for health professionals.

What are the ingredients in BLINCYTO?

Active ingredient: blinatumomab

Inactive ingredients: citric acid monohydrate, lysine hydrochloride, polysorbate 80, trehalose dihydrate, sodium hydroxide and preservative-free sterile water for injection.

Manufactured by: Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799

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For more information, go to www.blincyto.com or call Amgen at 1-800-772-6436.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 8/2016