BLINCYTO® (blinatumomab) for injection
35 mcg single-dose vial

For the treatment of MRD(+) B-cell precursor ALL

Immediately following frontline induction therapy, move beyond complete remission[1]

Zero in on MRD

BLINCYTO® converted most patients to MRD(–),* enabling them to live disease-free longer[1,2,†]

In the phase 2 BLAST study, BLINCYTO® converted 81% (n=70/86) of patients to MRD(–)[1,*]

*A complete MRD response, defined as the absence of detectable MRD confirmed in an assay with a minimum sensitivity of 0.01%.[1]

†Kaplan-Meier estimates with 2-sided 95% CIs were used to describe RFS; differences between subgroups were evaluated using log-rank test.[2]

ALL, acute lymphoblastic leukemia; CI, confidence interval; MRD, minimal residual disease; RFS, relapse-free survival.

INDICATION

- 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.
- This indication is approved under accelerated approval based on MRD response rate and hematological relapse-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

IMPORTANT SAFETY 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® and treat with corticosteroids as recommended.**
- **Neurological toxicities, which may be severe, life-threatening or fatal, occurred in patients receiving BLINCYTO®. Interrupt or discontinue BLINCYTO® as recommended.**

Click here to see full Prescribing Information, including **Boxed WARNINGS** and Medication Guide, for BLINCYTO®. Please see additional Important Safety Information throughout.

Engage the immune system with BLINCYTO®, a CD19-directed bispecific T cell engager[1]

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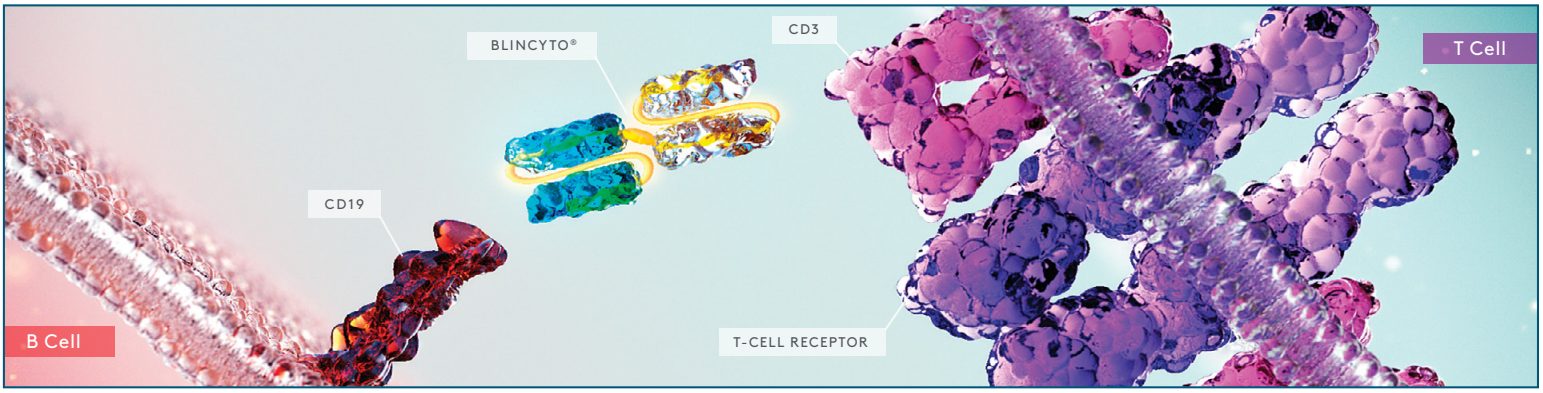
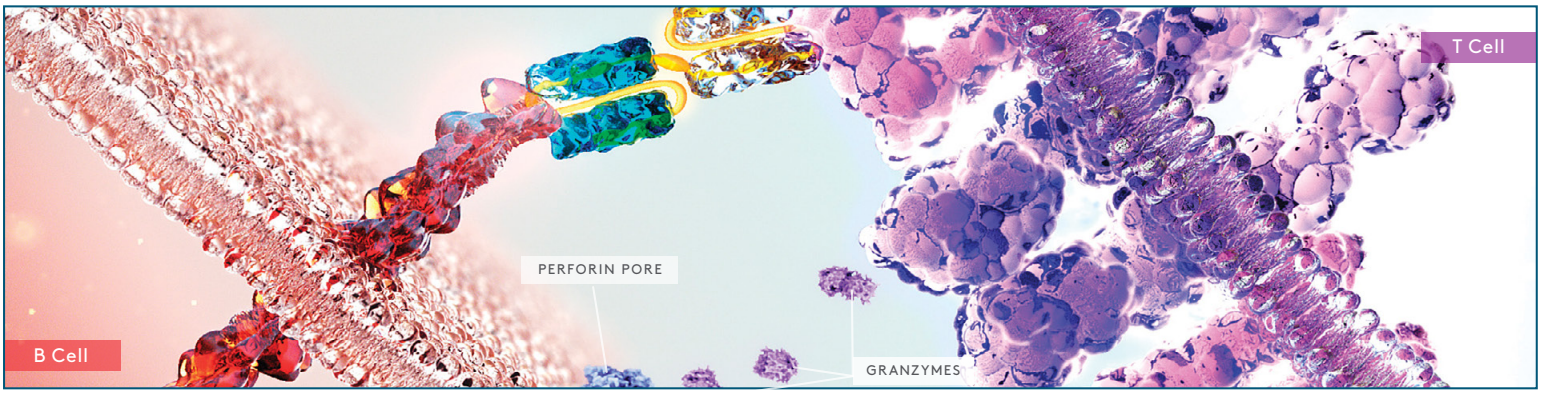
Target

BLINCYTO® activates endogenous T cells by connecting the CD3 antigen in the T-cell receptor complex with the CD19 surface antigen on benign and malignant B cells.[1]



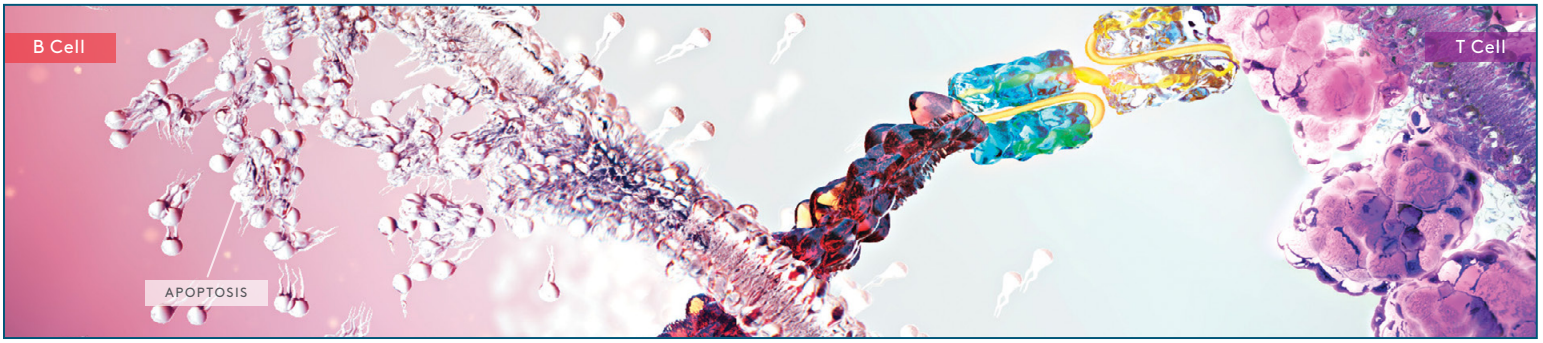
Engage

BLINCYTO® mediates the formation of a synapse between the T cell and the B cell, upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells.[1]



Activate

Inflammatory cytokine release and T-cell proliferation result in redirected CD19+ cell lysis.[1]



CD, cluster of differentiation.

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- Neurological toxicities, which may be severe, life-threatening or fatal, occurred in patients receiving BLINCYTO®. Interrupt or discontinue BLINCYTO® as recommended.

In the BLAST study, BLINCYTO® converted most patients to MRD(–)[1,2]

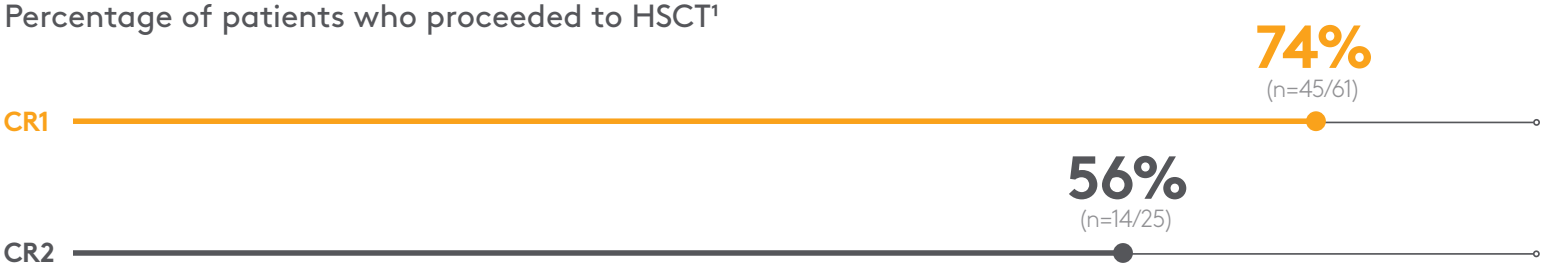
Primary endpoint: complete MRD response[1,2,†]

81%
(n=70/86)

of patients **had no detectable MRD[‡]**

- Complete MRD response was similar across patient subgroups (age, relapse history, and MRD burden)[1,2]

Percentage of patients who proceeded to HSCT[1]



Study design[1,2]

The BLAST study was a single-arm phase 2 study of BLINCYTO® treatment for adult patients with MRD(+) B-cell precursor ALL

Zero in on MRD[1] and intervene as early as CR1

[†]Defined as the absence of detectable MRD confirmed in an assay with a minimum sensitivity of 0.01% for 6 patients and ≤ 0.005% for 80 patients. Undetectable MRD was achieved by 65/80 patients with an assay sensitivity of at least 0.005%.[1]

[‡]Assessed after 1 treatment cycle.[1]

ALL, acute lymphoblastic leukemia; CR1, first complete remission; CR2, second complete remission; HSCT, allogeneic hematopoietic stem cell transplantation; MRD, minimal residual disease.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

- Cytokine Release Syndrome (CRS): CRS, which may be life-threatening or fatal, occurred in 15% of patients with R/R ALL and in 7% of patients with MRD-positive ALL. The median time to onset of CRS is 2 days after the start of infusion and the median time to resolution of CRS was 5 days among cases that resolved. Closely monitor and advise patients to contact their healthcare professional for signs and symptoms of serious adverse events such as fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased total bilirubin (TBILI), and disseminated intravascular coagulation (DIC). The manifestations of CRS after treatment with BLINCYTO® overlap with those of infusion reactions, capillary leak syndrome, and hemophagocytic histiocytosis/macrophage activation syndrome. 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.

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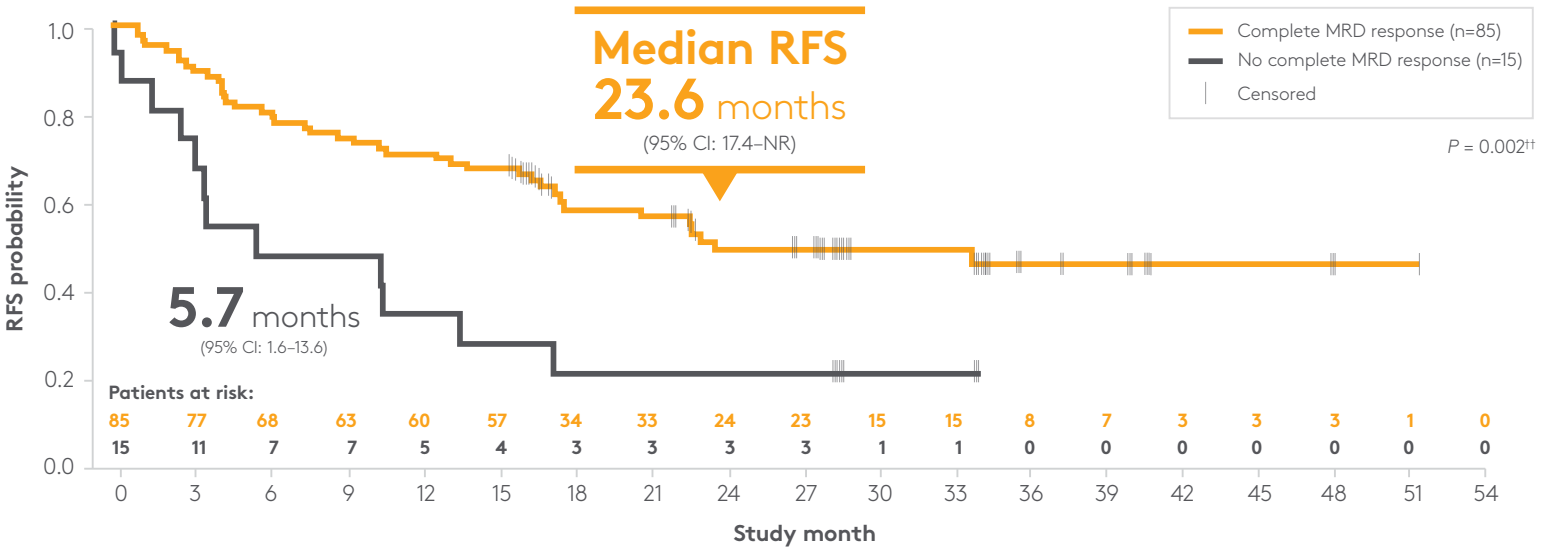
Patients[§,**] who converted to MRD(–) achieved significantly longer RFS[2,3]

RFS[††] in patients with vs without complete MRD response[‡‡,§§]



Patients treated with BLINCYTO® achieved nearly 3x longer RFS[1] when treated in CR1 vs CR2

Median RFS*** in patients[†††] who were MRD(+) treated in CR1 vs CR2

§ Patients in this population differ from the USPI population. Analysis includes the following additional patients: patients who achieved CRh* and CRi, and/or are in CR3.[1,2,4,5]

** Landmark analysis included patients in both the Key Secondary Endpoint Full Analysis Set and the Primary Endpoint Analysis Set from the BLAST study and excludes patients with an event (death or relapse) or censored before day 45 and patients without MRD results (n=1) or with insufficient sensitivity of the assay (n=2).[2]

†† Kaplan-Meier estimates with 2-sided 95% CIs were used to describe RFS; differences between subgroups were evaluated using log-rank test.[2]

‡‡ Of the patients in the Key Secondary Endpoint Full Analysis Set, 67% (74 out of 110) proceeded to HSCT in continuous remission, which is a potential confounder.[2]

§§ The median RFS was 23.6 months for MRD responders (n=70) vs 10.6 months for non-responders (n=16) based on an exploratory analysis of the USPI population. The assay used to assess MRD response had a sensitivity of 0.01% for 6 patients and ≤ 0.005% for 80 patients.[1,4]

*** Relapse was defined as either hematological or extramedullary relapse, secondary leukemia, or death due to any cause; includes time after transplantation; Kaplan-Meier estimate.[1]

††† 74% (45/61) of patients in CR1 and 56% (14/25) of patients in CR2 proceeded to HSCT.[1]

CI, confidence interval; CR3, third complete remission; CRh*, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; NR, not reached; RFS, relapse-free survival.

IMPORTANT SAFETY INFORMATION

- Neurological Toxicities: Approximately 65% of patients receiving BLINCYTO® in clinical trials experienced neurological toxicities. 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. Severe, life-threatening, or fatal neurological toxicities occurred in approximately 13% of patients, including encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Manifestations of neurological toxicity included cranial nerve disorders. Monitor patients for signs or symptoms and interrupt or discontinue BLINCYTO® as outlined in the PI.

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Majority of the most common adverse reactions (≥ 20% incidence) were mild to moderate[1,6]

Most common adverse reactions (≥ 20%) (N=137)[1,*]		
Adverse reaction	Any Grade[†] n (%)	≥ Grade 3[†] n (%)
General disorders and administration site conditions		
Pyrexia[‡]	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[§]	105 (77)	7 (5)
Nervous system disorders		
Headache	54 (39)	5 (4)
Tremor**	43 (31)	6 (4)

- Adverse reactions of Grade 3 or higher were reported in 64% of patients[1]
- The rate of neurologic events decreased over time in the BLAST study (47%, 24%, 15%, and 15% incidence in cycles 1, 2, 3, and 4, respectively)[2]
  - 36 patients (31%) interrupted treatment due to AEs, mainly neurologic events and flu-like symptoms[2]
  - Median time to resolution of any neurologic event was 4 days[2]

* The safety of BLINCYTO® in patients with MRD-positive B-cell precursor ALL was evaluated in two single-arm clinical studies with a total of 137 patients.[1]

† Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, in which Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe or medically significant but not immediately life-threatening, and Grade 4 is life-threatening.[1,6]

‡ Pyrexia includes body temperature increased and pyrexia.[1]

§ 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.[1]

** Tremor includes essential tremor, intention tremor, and tremor.[1]

AE, adverse event; ALL, acute lymphoblastic leukemia; MRD, minimal residual disease.

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Zero in on MRD and choose BLINCYTO®[1] as early as CR1

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The **first and only** FDA-approved therapy for patients with **MRD(+)** B-cell precursor ALL[1,7]

81%
(n=70/86)
Converted to MRD(–)[1,†,‡]

74%
(n=45/61)
Proceeded to HSCT[1] **in CR1**

23.6 months
(95% CI: 17.4–NR)
Median RFS
in patients[§,**] who converted to MRD(–)[2,††,‡‡,§§]

- Hospitalization is recommended[1] for the first **3 days** of cycle 1 and the first 2 days of cycle 2
- Majority of the most common adverse reactions (≥ 20% incidence) were **mild to moderate**[1,6,***]

† Defined as the absence of detectable MRD confirmed in an assay with a minimum sensitivity of 0.01% for 6 patients and ≤ 0.005% for 80 patients. Undetectable MRD was achieved by 65/80 patients with an assay sensitivity of at least 0.005%.[1]

‡ Assessed after 1 treatment cycle.[1]

§ Patients in this population differ from the USPI population. Analysis includes the following additional patients: patients who achieved CRh* and CRi, and/or are in CR3.[1,2,4,5]

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ALL, acute lymphoblastic leukemia; CI, confidence interval; CR1, first complete remission; CR3, third complete remission; CRh*, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; HSCT, allogeneic hematopoietic stem cell transplantation; MRD, minimal residual disease; NR, not reached; RFS, relapse-free survival.

IMPORTANT SAFETY INFORMATION

- Infections: Approximately 25% of patients receiving BLINCYTO® in clinical trials experienced serious infections such as sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site infections, some of which were life-threatening or fatal. Administer prophylactic antibiotics and employ surveillance testing as appropriate during treatment. Monitor patients for signs or symptoms of infection and treat appropriately, including interruption or discontinuation of BLINCYTO® as needed.
- Tumor Lysis Syndrome (TLS), which may be life-threatening or fatal, has been observed. Preventive measures, including pretreatment nontoxic cytoreduction and on-treatment hydration, should be used during BLINCYTO® treatment. Monitor patients for signs and symptoms of TLS and interrupt or discontinue BLINCYTO® as needed to manage these events.
- Neutropenia and Febrile Neutropenia, including life-threatening cases, have been observed. Monitor appropriate laboratory parameters (including, but not limited to, white blood cell count and absolute neutrophil count) during BLINCYTO® infusion and interrupt BLINCYTO® if prolonged neutropenia occurs.

Please see additional safety information, including **Boxed WARNINGS**, throughout.

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- **Neurological toxicities, which may be severe, life-threatening or fatal, occurred in patients receiving BLINCYTO®. Interrupt or discontinue BLINCYTO® as recommended.**

Contraindications

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

Warnings and Precautions

- Cytokine Release Syndrome (CRS): CRS, which may be life-threatening or fatal, occurred in 15% of patients with R/R ALL and in 7% of patients with MRD-positive ALL. The median time to onset of CRS is 2 days after the start of infusion and the median time to resolution of CRS was 5 days among cases that resolved. Closely monitor and advise patients to contact their healthcare professional for signs and symptoms of serious adverse events such as fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased total bilirubin (TBILI), and disseminated intravascular coagulation (DIC). The manifestations of CRS after treatment with BLINCYTO® overlap with those of infusion reactions, capillary leak syndrome, and hemophagocytic histiocytosis/macrophage activation syndrome. 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.
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- Neutropenia and Febrile Neutropenia, including life-threatening cases, have been observed. Monitor appropriate laboratory parameters (including, but not limited to, white blood cell count and absolute neutrophil count) during BLINCYTO® infusion and interrupt BLINCYTO® if prolonged neutropenia occurs.
- Effects on Ability to Drive and Use Machines: Due to the possibility of neurological events, including seizures, patients receiving BLINCYTO® are at risk for loss of consciousness, and should be advised against driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO® is being administered.
- Elevated Liver Enzymes: Transient elevations in liver enzymes have been associated with BLINCYTO® treatment with a median time to onset of 3 days. In patients receiving BLINCYTO®, although the majority of these events were observed in the setting of CRS, some cases of elevated liver enzymes were observed outside the setting of CRS, with a median time to onset of 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 ALT, AST, gamma-glutamyl transferase, and TBILI prior to the start of and during BLINCYTO® treatment. BLINCYTO® treatment should be interrupted if transaminases rise to > 5 times the upper limit of normal (ULN) or if TBILI rises to > 3 times ULN.
- 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 and interrupt or discontinue BLINCYTO® and dexamethasone as needed.
- Leukoencephalopathy: Although the clinical significance is unknown, cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving BLINCYTO®, especially in patients previously treated with cranial irradiation and antileukemic chemotherapy.

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IMPORTANT SAFETY INFORMATION (cont'd)

- Preparation and administration errors have occurred with BLINCYTO® treatment. Follow instructions for preparation (including admixing) and administration in the PI strictly to minimize medication errors (including underdose and overdose).
- Immunization: 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®.
- Risk of Serious Adverse Reactions in Pediatric Patients due to Benzyl Alcohol Preservative: Serious and fatal adverse reactions including "gasping syndrome," which is characterized by central nervous system depression, metabolic acidosis, and gasping respirations, can occur in neonates and infants treated with benzyl alcohol-preserved drugs including BLINCYTO® (with preservative). When prescribing BLINCYTO® (with preservative) for pediatric patients, consider the combined daily metabolic load of benzyl alcohol from all sources including BLINCYTO® (with preservative) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known. Due to the addition of bacteriostatic saline, 7-day bags of BLINCYTO® solution for infusion with preservative contain benzyl alcohol and are not recommended for use in any patients weighing < 22 kg.

Adverse Reactions

- The most common adverse reactions (≥ 20%) in clinical trial experience of patients with MRD-positive B-cell precursor ALL (BLAST Study) treated with BLINCYTO® were pyrexia (91%), infusion-related reactions (77%), headache (39%), infections (pathogen unspecified [39%]), tremor (31%), and chills (28%). 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 that were observed more frequently (≥ 10%) in the pediatric population compared to the adults with relapsed or refractory B-cell precursor ALL 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%).

Dosage and Administration Guidelines

- BLINCYTO® is administered as a continuous intravenous infusion at a constant flow rate using an infusion pump which should be programmable, lockable, non-elastomeric, and have an alarm.
- It is very important that the instructions for preparation (including admixing) and administration provided in the full Prescribing Information are strictly followed to minimize medication errors (including underdose and overdose).

References: 1. BLINCYTO® (blinatumomab) prescribing information, Amgen. **2.** Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood*. 2018;131:1522-1531. **3.** Food and Drug Administration. BLINCYTO® (blinatumomab) for minimal residual disease positive (MRD+) B-cell precursor acute lymphoblastic leukemia (ALL). https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM603411.pdf. Accessed April 27, 2019. **4.** Data on file, Amgen; 2018. **5.** Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-precursor acute lymphoblastic leukemia. *Blood*. 2018;131:1522-1531. Appendix, Supplementary Appendix; http://www.bloodjournal.org/content/bloodjournal/suppl/2018/01/22/blood-2017-08-798322.DC1/blood-2017-08-798322-1.pdf. Accessed April 27, 2019. **6.** National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed April 27, 2019. **7.** Food and Drug Administration. FDA expands approval of Blincyto for treatment of a type of leukemia in patients who have a certain risk factor for relapse. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm603151.htm. Accessed April 27, 2019.

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AMGEN®

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