BLINCYTO® dose adjustments for adverse reactions

See below for instructions on how to adjust BLINCYTO® dosing if patients experience adverse reactions during treatment.

Interruption after an adverse reaction

≤ 7 days **Continue the same cycle of BLINCYTO®**
28 days total—including days before and after interruption

> 7 days **Start a new cycle of BLINCYTO®**

ADVERSE REACTION	GRADE*	PATIENTS WEIGHING ≥ 45 kg	PATIENTS WEIGHING < 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 5 mg/m^2 (maximum 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 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. **Restart** BLINCYTO® at 9 mcg/day. **Escalate** to 28 mcg/day after 7 days if the adverse reaction does not recur. **Discontinue** BLINCYTO® permanently if the adverse reaction occurred at 9 mcg/day, or if the adverse reaction takes more than 7 days to resolve.	**Withhold** BLINCYTO® until no more than Grade 1 (mild) and for at least 3 days. **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. **Discontinue** BLINCYTO® permanently if the adverse reaction occurred at 5 mcg/m^2/day, or if the adverse reaction takes more than 7 days to resolve.
	Grade 4	**Discontinue** BLINCYTO® permanently.	
Other Clinically Relevant Adverse Reactions	Grade 3	**Withhold** BLINCYTO® until no more than Grade 1 (mild). **Restart** BLINCYTO® at 9 mcg/day. **Escalate** to 28 mcg/day after 7 days if the adverse reaction does not recur. **Discontinue** BLINCYTO® permanently if the adverse reaction takes more than 14 days to resolve.	**Withhold** BLINCYTO® until no more than Grade 1 (mild). **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. **Discontinue** BLINCYTO® permanently if the adverse reaction takes more than 14 days to resolve.
	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.

INDICATION

BLINCYTO® is indicated for the treatment of relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.

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.**

Contraindications

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

Click here to see full Prescribing Information, including **Boxed WARNINGS** and Medication Guide, for BLINCYTO®. Please see additional Important Safety Information on page 2.

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

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.
- 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.
- 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.
- 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.
- 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 Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (TOWER Study) treated with BLINCYTO® 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 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).

Please see additional Important Safety Information, including **Boxed WARNINGS**, on the front.

Please see Prescribing Information.

Reference: BLINCYTO® (blinatumomab) prescribing information, Amgen.

AMGEN®

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