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.

INDICATIONS

BLINCYTO® (blinatumomab) is indicated for the treatment of CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adult and pediatric patients one month and older with:

- Philadelphia chromosome-negative disease in the consolidation phase of multiphase chemotherapy
- Minimal residual disease (MRD) greater than or equal to 0.1% in first or second complete remission
- Relapsed or refractory disease

IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

- **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, including immune effector cell-associated neurotoxicity syndrome (ICANS) 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 patients receiving BLINCYTO®. 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, and disseminated intravascular coagulation (DIC). The manifestations of CRS after treatment with BLINCYTO® overlap with those of infusion reactions, capillary leak syndrome (CLS), and hemophagocytic histiocytosis/macrophage activation syndrome (MAS). Using all of these terms to define CRS in clinical trials of BLINCYTO, CRS was reported in 15% of patients with R/R ALL, in 7% of patients with MRD-positive ALL, and in 16% of patients receiving BLINCYTO® cycles in the consolidation phase of therapy. 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, including Immune Effector Cell-Associated Neurotoxicity Syndrome:** BLINCYTO® can cause serious or life-threatening neurologic toxicity, including ICANS. The incidence of neurologic toxicities in clinical trials was approximately 65%. The median time to the first event was within the first 2 weeks of BLINCYTO® treatment. The most common (≥ 10%) manifestations of neurological toxicity were headache and tremor. Grade 3 or higher 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. The majority of neurologic toxicities resolved following interruption of BLINCYTO®, but some resulted in treatment discontinuation.

  The incidence of signs and symptoms consistent with ICANS in clinical trials was 7.5%. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. 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 studies. Patients with Down Syndrome over the age of 10 years may have a higher risk of seizures with BLINCYTO® therapy.

  Monitor patients for signs and symptoms of neurological toxicities, including ICANS, and interrupt or discontinue BLINCYTO® as outlined in the PI. Advise outpatients to contact their healthcare professional if they develop signs or symptoms of neurological toxicities.
- **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 and ICANS, 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 total blood bilirubin 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 total bilirubin 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®.
- **Benzyl Alcohol Toxicity in Neonates:** Serious adverse reactions, including fatal reactions and the "gasping syndrome," have been reported in very low birth weight (VLBW) neonates born weighing less than 1500 g, and early preterm neonates (infants born less than 34 weeks gestational age) who received intravenous drugs containing benzyl alcohol as a preservative. Early preterm VLBW neonates may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol.

  Use the preservative-free preparations of BLINCYTO® where possible in neonates. When prescribing BLINCYTO® (with preservative) for neonatal patients, consider the combined daily metabolic load of benzyl alcohol from all sources including BLINCYTO® (with preservative), other products containing benzyl alcohol or other excipients (e.g., ethanol, propylene glycol) which compete with benzyl alcohol for the same metabolic pathway.

  Monitor neonatal patients receiving BLINCYTO® (with preservative) for new or worsening metabolic acidosis. The minimum amount of benzyl alcohol at which serious adverse reactions may occur in neonates is not known. The BLINCYTO® 7-Day bag (with preservative) contains 7.4 mg of benzyl alcohol per mL
- **Embryo-Fetal Toxicity:** Based on its mechanism of action, BLINCYTO® may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with BLINCYTO® and for 48 hours after the last dose.

Adverse Reactions

- The safety of BLINCYTO® in adult and pediatric patients one month and older with MRD-positive B-cell precursor ALL (n=137), relapsed or refractory B-cell precursor ALL (n=267), and Philadelphia chromosome-negative B cell precursor ALL in consolidation (n=165) was evaluated in clinical studies. The most common adverse reactions (≥ 20%) to BLINCYTO® in this pooled population were pyrexia, infusion-related reactions, headache, infection, musculoskeletal pain, neutropenia, nausea, anemia, thrombocytopenia, and diarrhea.

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 BLINCYTO® full Prescribing Information, including BOXED WARNINGS.

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

AMGEN®

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