Blincyto® (blinatumomab**)**

Brief Prescribing Information Refer to the Summary of Product Characteristics before prescribing Blincyto.**Pharmaceutical Form:** One Blincyto 35mcg 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 not use the IV Solution Stabilizer to reconstitute BLINCYTO. **Clinical Particulars: Therapeutic indications: MRD-positive B-cell precursor ALL:** BLINCYTO is indicated for the treatment of CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission (CR) with minimal residual disease (MRD) greater than or equal to 0.1% in adults and pediatric patients one month and older. **Relapsed or refractory B-cell precursor ALL:** BLINCYTO is indicated for the treatment of relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in adults and pediatric patients one month and older. **B-cell Precursor ALL in the Consolidation Phase:** BLINCYTO is indicated for the treatment of CD19-positive Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia (ALL) in the consolidation phase of multiphase chemotherapy in adult and pediatric patients one month and older. **Posology and method of administration**: **Treatment of MRD-positive B-cell Precursor ALL**: A treatment course consists of 1 cycle of BLINCYTO for induction followed by up to 3 additional cycles for consolidation. A single cycle of treatment of BLINCYTO induction or consolidation consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days). Refer to the full SmPC for the recommended dose by patient weight and schedule. Patients weighing 45 kg or more receive a fixed-dose. For patients weighing less than 45 kg, the dose is calculated using the patient's body surface area (BSA). Hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiations (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended. Intrathecal chemotherapy prophylaxis is recommended before and during BLINCYTO therapy to prevent central nervous system ALL relapse. Premedicate with prednisone or equivalent for MRD-positive B-cell Precursor ALL For adult patients, premedicate with prednisone 100 mg intravenously or equivalent (e.g., dexamethasone 16 mg) 1 hour prior to the first dose of BLINCYTO in each cycle. For pediatric patients, premedicate with 5 mg/m^2 of dexamethasone intravenously or orally, to a maximum dose of 20 mg prior to the first dose of BLINCYTO in the first cycle and when restarting an infusion after an interruption of 4 or more hours in the first cycle. For administration of BLINCYTO, refer to Pharmaceutical Particulars in SmPC. **Treatment of Relapsed or Refractory B-cell Precursor ALL**: A treatment course consists of up to 2 cycles of BLINCYTO for induction followed by 3 additional cycles for consolidation and up to 4 additional cycles of continued therapy. A single cycle of treatment of BLINCYTO induction or consolidation consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days). A single cycle of treatment of BLINCYTO continued therapy consists of 28 days of continuous intravenous infusion followed by a 56-day treatment-free interval (total 84 days). Refer to the full SmPC for the recommended dose by patient weight and schedule. Patients weighing 45 kg or more receive a fixed-dose and for patients weighing less than 45 kg, the dose is calculated using the patient's (BSA). Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiation (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended. Intrathecal chemotherapy prophylaxis is recommended before and during BLINCYTO therapy to prevent central nervous system ALL relapse. Premedicate with dexamethasone: For adult patients, premedicate with 20 mg of dexamethasone intravenously or orally 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 intravenously or orally, 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. For administration of BLINCYTO, refer to Pharmaceutical Particulars in SmPC. **Treatment of B-cell Precursor ALL in the Consolidation Phase:** A single cycle of BLINCYTO monotherapy in consolidation is 28 days of continuous infusion followed by a 14-day treatment-free interval (total 42 days). Patients weighing 45 kg or more receive a fixed-dose, and for patients weighing less than 45 kg, the dose is calculated using the patient's BSA. Refer to the full SmPC for the recommended dose by patient weight and schedule. Hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and reinitiation (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended. Intrathecal chemotherapy prophylaxis is recommended before and during BLINCYTO therapy to prevent central nervous system ALL relapse. Premedicate with dexamethasone: For adult patients, premedicate with dexamethasone 20 mg intravenously within 1 hour prior to the first dose of BLINCYTO of each cycle. For pediatric patients, premedicate with 5 mg/m2 of dexamethasone intravenously or orally, to a maximum dose of 20 mg prior to the first dose of BLINCYTO in the first cycle and when restarting an infusion after an interruption of 4 or more hours in the first cycle. For administration of BLINCYTO, refer to Pharmaceutical Particulars in SmPC. Special populations: *Pediatric use*: The safety and efficacy of BLINCYTO in pediatric patients less than 1 month of age have not been established for any indication. Minimal Residual Disease (MRD)-Positive B-cell Precursor ALL: The safety and efficacy of BLINCYTO for the treatment of CD19-positive 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% have been established in pediatric patients one month and older. Use of BLINCYTO is supported by evidence from two randomized, controlled trials (Study AALL1331 and Study 20120215) (see section **Undesirable effects** in *SmPC for more details*) in pediatric patients with first relapsed B-cell precursor ALL. Both studies included pediatric patients with MRD-positive B-cell precursor ALL. The studies included pediatric patients treated with BLINCYTO in the following age groups: 6 infants (1 month up to less than 2 years), 165 children (2 years up to less than 12 years), and 70 adolescents (12 years to less than 17 years). In general, the adverse reactions in BLINCYTO-treated pediatric patients were similar in type to those seen in adult patients with MRD-positive ALL, see section **Undesirable effects** in *SmPC for more details*, and no differences in safety were observed between the different pediatric age subgroups. Relapsed or Refractory B-cell Precursor ALL: The safety and efficacy of BLINCYTO have been established in pediatric patients one month and older with relapsed or refractory B-cell precursor ALL. Use of BLINCYTO is supported by a 6 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, see section **Clinical efficacy and safety** in SmPC for more details. Adverse reactions that were observed more frequently (≥ 10% difference) in the pediatric population compared to the adult population were pyrexia (80% vs. 61%), hypertension (26% vs. 8%), anemia (41% vs. 24%), infusion-related reaction (49% vs. 34%), thrombocytopenia (34% vs. 21%), leukopenia (24% vs.11%), and weight increased (17% vs. 6%). In pediatric patients less than 2 years old (infants) with relapsed or refractory ALL, 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%). B-cell Precursor ALL in the Consolidation Phase: The safety and efficacy of BLINCYTO for the treatment of Philadelphia chromosome-negative B-cell precursor ALL in the consolidation phase have been established in pediatric patients one month and older. Use of BLINCYTO for this indication is supported by extrapolation from a randomized controlled study in adults (Study E1910) and evidence from two randomized, controlled studies in pediatric patients (Study 20120215 and Study AALL1331) see sections **Undesirable effects**, **Posology and method of administration**, **Pharmacokinetic properties** and **Clinical efficacy and safety** in SmPC for more details.. Benzyl Alcohol toxicity in Neonates: Serious and fatal adverse reactions, including "gasping syndrome", can occur in very low birth weight (VLBW) neonates born weighing less than 1,500 g, and early preterm neonates (infants born less than 34 weeks gestational age) treated with benzyl alcohol-preserved drugs intravenously. The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. In these cases, benzyl alcohol dosages of 99 to 234 mg/kg/day produced high concentrations of benzyl alcohol and its metabolite in the blood and urine (blood concentration of benzyl alcohol were 0.61 to 1.378 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. The minimum amount of benzyl alcohol at which serious adverse reactions may occur in neonates is not known, see section **Special warnings and precautions for use** in SmPC for more details. Use the preservative-free formulations of BLINCYTO where possible in neonates. When prescribing BLINCYTO (with preservative) in neonatal patients, consider the combined daily metabolic load of benzyl alcohol from all sources including BLINCYTO (with preservative). The BLINCYTO 7-Day bag (with preservative) contains 7.4 mg of benzyl alcohol per mL, see section **Special warnings and precautions for use** in SmPC for more details. Benzyl alcohol administration may contribute to metabolic acidosis in pediatric patients, particularly those with immaturity of the metabolic pathway for alcohol, or those with underlying conditions or receiving concomitant medications that could predispose to acid base imbalance. Monitor these patients during use of BLINCYTO (with preservative) for new or worsening metabolic acidosis. *Geriatric use*: There were 158 (7%) patients 65 years and older in clinical studies of BLINCYTO for patients with MRD-positive, CD19-positive B-cell precursor ALL in first or second complete remission, relapsed or refractory CD19-positive B-cell precursor ALL, and CD19-positive, Philadelphia chromosome-negative B-cell precursor ALL in the consolidation phase. Of the total number of BLINCYTO-treated patients in these studies, 123 (8%) were 65 years of age and older and 21 (1%) were 75 years of age or older. No overall differences in safety

or effectiveness were observed between these patients and younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, elderly patients experienced a higher rate of serious infections and neurological toxicities, including cognitive disorder, encephalopathy, and confusion, see section **Special warnings and precautions for use** in SmPC for more details. **Dosage Modifications for Adverse Reactions**: If the interruption after an adverse reaction is no longer than 7 days, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse reaction is longer than 7 days, start a new cycle. **Contraindications:** BLINCYTO is contraindicated in patients with known hypersensitivity to blinatumomab or to any component of the product formulation. **Special warnings and precautions for use**: Cytokine Release Syndrome: Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. The median time to onset of CRS was 2 days after the start of infusion and the median time to resolution of CRS was 5 days among cases that resolved. Manifestations of CRS include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased total bilirubin, and disseminated intravascular coagulation (DIC). The manifestations of CRS after treatment with BLINCYTO overlap with those of infusion reactions, capillary leak syndrome (CLS), and hemophagocytic histiocytosis/macrophage activation syndrome (MAS). Using all of these terms to define CRS in clinical trials of BLINCYTO, CRS was reported in 15% of patients with relapsed or refractory ALL in 7% of patients with MRD-positive ALL, and in 16% of patients receiving BLINCYTO cycles in the consolidation phase of therapy, see section **Undesirable effects** in *SmPC* for more details. Monitor patients for signs or symptoms of these events. Advise outpatients on BLINCYTO to contact their healthcare professional for signs and symptoms associated with CRS. If severe CRS occurs, interrupt BLINCYTO until CRS resolves. Discontinue BLINCYTO permanently if life-threatening CRS occurs. Administer corticosteroids for severe or life-threatening CRS, see section **Posology and method of administration** in *SmPC* for more details. Neurological Toxicities including Immune Effector Cell-Associated Neurotoxicity Syndrome: BLINCYTO can cause serious or life-threatening neurologic toxicity, including ICANS see section **Undesirable effects** in *SmPC* for more details. The incidence of neurologic toxicities in clinical trials was approximately 65% *[*see section **Adverse Reactions** *in SmPC* for more details]. Among patients that experienced a neurologic toxicity, 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; the neurological toxicity profile varied by age group *[see Use in Specific Populations (8.4, 8.5)]*. Grade 3 or higher neurological toxicities following initiation of BLINCYTO administration occurred in approximately 13% of patients and included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Manifestations of neurological toxicity included cranial nerve disorders. The majority of neurologic 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. BLINCYTO can cause serious or life-threatening neurologic toxicity, including ICANS *[*see section ***Adverse Reactions*** *in SmPC* for more details*]*. 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 receiving BLINCYTO for signs and symptoms of neurological toxicities, including ICANS. Advise outpatients on BLINCYTO to contact their healthcare professional if they develop signs or symptoms of neurological toxicities. Interrupt or discontinue BLINCYTO as recommended, see section **Posology and method of administration** in *SmPC* for more details. Infections: In patients with ALL receiving BLINCYTO in clinical studies, serious infections such as sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site infections were observed in approximately 25% of patients, some of which were life-threatening or fatal, see section **Undesirable effects** in *SmPC* for more details. As appropriate, administer prophylactic antibiotics and employ surveillance testing during treatment with BLINCYTO. Monitor patients for signs and symptoms of infection and treat appropriately. 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 section **Posology and method of administration** in *SmPC* for more details. Neutropenia and Febrile Neutropenia: Neutropenia and febrile neutropenia, including life-threatening cases, have been observed in patients receiving BLINCYTO, see section **Undesirable effects** in *SmPC* for more details. 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. Elevated Liver Enzymes: Treatment with BLINCYTO was associated with transient elevations in liver enzymes, see section **Undesirable effects** in *SmPC* for more details in *SmPC* for more details. In patients with ALL receiving BLINCYTO in clinical studies, the median time to onset of elevated liver enzymes was 3 days. The majority of these transient elevations in liver enzymes were observed in the setting of CRS. For the events that were observed outside the setting of CRS, the median time to onset was 19 days. Grade 3 or greater elevations in liver enzymes occurred in approximately 7% of patients outside the setting of CRS and resulted in treatment discontinuation in less than 1% of patients. Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during BLINCYTO treatment. Interrupt BLINCYTO if the transaminases rise to greater than 5 times the upper limit of normal or if total bilirubin rises to more than 3 times the upper limit of normal. Pancreatitis: Fatal pancreatitis has been reported in patients receiving BLINCYTO in combination with dexamethasone in clinical studies and the postmarketing setting, see section **Undesirable effects** in *SmPC* for more details. Evaluate patients who develop signs and symptoms of pancreatitis. Management of pancreatitis may require either temporary interruption or discontinuation of BLINCYTO and dexamethasone, see section **Posology and method of administration** in *SmPC* for more details. 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. 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 section **Special precautions for disposal and other handling** in *SmPC* for more details. 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. Risk of Serious Adverse Reactions in Pediatric Patients due to Benzyl Alcohol Preservative: Serious adverse reactions, including fatal reactions and the "gasping syndrome", have been reported in very low birth weight (VLBW) neonates born weighing less than 1,500 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, see section **Posology and method of administration** in *SmPC* for more details. 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. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known, refer to full SmPC for more details. Due to the addition of bacteriostatic saline, 7-day infusion bags of BLINCYTO solution contain benzyl alcohol and are not recommended for use in any patients weighing less than 22 kg, see section **Posology and method of administration** in *SmPC* for more details. 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, see section **Fertility, Pregnancy and Lactation** in *SmPC* for more details. **Interaction with other medicinal products and other forms of interaction**: No formal drug interaction studies have been conducted with BLINCYTO. Initiation of BLINCYTO treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug- drug interaction risk is during the first 9 days of the first cycle and the first 2 days of the second cycle in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity (e.g., warfarin) or drug concentrations (e.g., cyclosporine). Adjust the dose of the concomitant drug as needed, see section **Pharmacodynamic properties** and **Clinical efficacy and safety** in *SmPC* for more details. **Fertility, Pregnancy and Lactation:** 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 section **Pharmacodynamic properties** in *SmPC* for more details. There are no data on the use of BLINCYTO in pregnant women. In animal reproduction studies, a murine surrogate molecule administered to pregnant mice crossed the placental barrier (see Data). Advise pregnant women of the potential risk to a fetus. The background rate of major birth defects and miscarriage is unknown for the indicated population. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. Blinatumomab causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance. In addition, based on expression of CD19 on B-cells and the finding of B-cell depletion

in non-pregnant animals, blinatumomab can cause B-cell lymphocytopenia in infants exposed to blinatumomab *in-utero*. 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 section **Special warnings and precautions for use** in *SmPC* for more details. 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. Lactation: *Risk Summary*: There is no information regarding the presence of blinatumomab in human milk, the effects on the breastfed infant, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breastfed infants from BLINCYTO, including B-cell lymphocytopenia, advise patients not to breastfeed during treatment with BLINCYTO and for 48 hours after the last dose. Females and Males of Reproductive Potential: BLINCYTO may cause fetal harm when administered to a pregnant woman, see section **Fertility, Pregnancy and Lactation** in *SmPC* for more details. Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to initiating BLINCYTO treatment. Contraception: Advise females of reproductive potential to use effective contraception during treatment with BLINCYTO and for 48 hours after the last dose. Fertility: No studies have been conducted to evaluate the effects of blinatumomab on fertility. There were no effects on male or female mouse reproductive organs in 13-week toxicity studies with the murine surrogate molecule, see section **Pharmacokinetic properties** in *SmPC* for more details. **Effects on ability to drive and use machines**: Due to the potential for neurologic events, including seizures and ICANS, patients receiving BLINCYTO are at risk for loss of consciousness, see section **Special warnings and precautions for use** in *SmPC* for more details. 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. **Undesirable effects**: refer to the SmPC for full details about the undesirable effect. Cytokine Release Syndrome, Neurological Toxicities, Infections, Tumor Lysis Syndrome, Neutropenia and Febrile Neutropenia, Effects on Ability to Drive and Use Machines, Elevated Liver Enzymes, Pancreatitis, Leukoencephalopathy. Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. ***MRD-positive B-cell Precursor ALL:*** The safety of BLINCYTO in patients with MRD-positive B-cell precursor ALL was evaluated in two single-arm clinical studies in which 137 patients were treated with BLINCYTO. The median age of the study population was 45 years (range: 18 to 77 years). The most common adverse reactions (≥ 20%) were pyrexia, infusion-related reactions, headache, infections (pathogen unspecified), tremor, and chills. Serious adverse reactions were reported in 61% of patients. The most common serious adverse reactions (≥ 2%) included pyrexia, tremor, encephalopathy, aphasia, lymphopenia, neutropenia, overdose, device related infection, seizure, and staphylococcal infection. Adverse reactions of Grade 3 or higher were reported in 64% of patients. Discontinuation of therapy due to adverse reactions occurred in 17% of patients; neurologic events were the most frequently reported reasons for discontinuation. There were 2 fatal adverse reactions that occurred within 30 days of the end of BLINCYTO treatment (atypical pneumonia and subdural hemorrhage), refer to the SmPC for the full details. ***Relapsed or Refractory B-cell Precursor ALL:***. The most common adverse reactions (≥ 20%) in the BLINCYTO arm were infections (bacterial and pathogen unspecified), pyrexia, headache, infusion-related reactions, anemia, febrile neutropenia, thrombocytopenia, and neutropenia. Serious adverse reactions were reported in 62% of patients. The most common serious adverse reactions (≥ 2%) included febrile neutropenia, pyrexia, sepsis, pneumonia, overdose, septic shock, CRS, bacterial sepsis, device related infection, and bacteremia. Adverse reactions of Grade 3 or higher were reported in 87% of patients. Discontinuation of therapy due to adverse reactions occurred in 12% of patients treated with BLINCYTO; neurologic events and infections were the most frequently reported reasons for discontinuation of treatment due to an adverse reaction. Fatal adverse events occurred in 16% of patients. The majority of the fatal events were infections. Refer to the SmPC for the full details. Other important adverse reactions from pooled relapsed or refractory B-cell precursor ALL studies were: ***Blood and lymphatic system disorders:*** lymphadenopathy, hematophagic histiocytosis, and leukocytosis (includes leukocytosis and white blood cell count increased). ***General disorders and administration site conditions:*** chills, chest pain (includes chest discomfort, chest pain, musculoskeletal chest pain, and non-cardiac chest pain), pain, body temperature increased, hyperthermia, and systemic inflammatory response syndrome. ***Hepatobiliary disorders:*** hyperbilirubinemia (includes blood bilirubin increased and hyperbilirubinemia). ***Immune system disorders:*** hypersensitivity (includes hypersensitivity, anaphylactic reaction, angioedema, dermatitis allergic, drug eruption, drug hypersensitivity, erythema multiforme, and urticaria). ***Injury, poisoning and procedural complications:*** medication error and overdose (includes overdose, medication error, and accidental overdose)**.** ***Investigations:*** weight increased, decreased immunoglobulins (includes immunoglobulins decreased, blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, and hypogammaglobulinemia), blood alkaline phosphatase increased, and hypertransaminasemia. ***Metabolism and nutrition disorders:*** tumor lysis syndrome ***Musculoskeletal and connective tissue disorders:*** back pain, bone pain, and pain in extremity**.** ***Nervous system disorders:*** tremor (resting tremor, intention tremor, essential tremor, and tremor), altered state of consciousness (includes altered state of consciousness, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, stupor, and somnolence), dizziness, memory impairment, seizure (includes seizure and atonic seizure), aphasia, cognitive disorder, speech disorder, hypoesthesia, encephalopathy, paresthesia and cranial nerve disorders (trigeminal neuralgia, trigeminal nerve disorder, sixth nerve paralysis, cranial nerve disorder, facial nerve disorder, and facial paresis)**.** ***Psychiatric disorders:*** insomnia, disorientation, confusional state, and depression (includes depressed mood, depression, suicidal ideation, and completed suicide)**.** ***Respiratory, thoracic and mediastinal disorders:*** dyspnea (includes acute respiratory failure, dyspnea, dyspnea exertional, respiratory failure, respiratory distress, bronchospasm, bronchial hyperreactivity, tachypnea, and wheezing), cough, and productive cough. ***Vascular disorders:*** hypotension (includes blood pressure decreased, hypotension, hypovolemic shock, and circulatory collapse), hypertension (includes blood pressure increased, hypertension, and hypertensive crisis), flushing (includes flushing and hot flush), and capillary leak syndrome**.** ***B-cell Precursor ALL in the Consolidation Phase*** Study E1910 The safety of a consolidation regimen comprised of multiple cycles of BLINCYTO monotherapy in addition to multiple cycles of chemotherapy (BLINCYTO arm) was evaluated in a randomized trial in adult patients with newly diagnosed Philadelphia chromosome-negative B-cell precursor ALL (Study E1910) (see section **Clinical efficacy and safety** in *SmPC* for more details) which included 111 patients treated in the BLINCYTO arm and 112 patients treated in the chemotherapy alone arm. In the BLINCYTO arm, the median (range) of cycles was 8 (1-8) (4 cycles of BLINCYTO and 4 cycles of chemotherapy). In the chemotherapy alone arm, the median (range) of cycles was 4 (1-4). The most common (≥ 20%) adverse reactions during consolidation cycles in the BLINCYTO arm were neutropenia, thrombocytopenia, anemia, leukopenia, headache, infection, nausea, lymphopenia, diarrhea, musculoskeletal pain, and tremor. The adverse reactions occurring at a difference between arms in incidence of ≥ 10% for All Grades or ≥ 5% for Grade 3 or higher, are summarized in SmPC. *Study 20120215. The* safety of BLINCYTO as the 3rd cycle of the consolidation phase was evaluated in a randomized, open-label study (Study 20120215) following induction and two cycles of consolidation chemotherapy in pediatric and young adult patients with high-risk first-relapsed B-cell precursor ALL, see section **Clinical efficacy and safety** in *SmPC* for more details. The study included 54 patients treated with one cycle of BLINCYTO and 52 patients treated with one cycle of chemotherapy. Serious adverse reactions occurred in 28% of patients who received BLINCYTO. Permanent discontinuation of BLINCYTO due to an adverse reaction occurred in 4% of patients. Adverse reactions that led to discontinuation included nervous system disorder and seizure. Dosage interruptions of BLINCYTO due to an adverse reaction occurred in 11% of patients. Adverse reactions which required dosage interruption in > 2% of patients included nervous system disorder. The most common (≥ 20%) adverse reactions in the BLINCYTO arm were pyrexia, nausea, headache, rash, hypogammaglobulinemia, and anemia. The adverse reactions occurring at a difference of ≥ 10% incidence for any grade or at a difference of ≥ 5% incidence for Grade 3 or 4 between the BLINCYTO arm and chemotherapy arm are summarized in SmPC.. **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. **Overdose:** Overdoses have been observed, including one adult patient who received 133-fold the recommended therapeutic dose of BLINCYTO delivered over a short duration. In the dose evaluation phase of a study in pediatric and adolescent patients with relapsed or refractory B-cell precursor ALL, one 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 section **Special warnings and precautions for use** and **Undesirable effects** in *SmPC* for more details. Overdoses resulted in adverse reactions, which were consistent with the reactions observed at the recommended dosage and included fever, tremors, and headache. In the event of overdose, interrupt the infusion, monitor the patient for signs of adverse reactions, and provide supportive care. Consider re-initiation of BLINCYTO at the recommended dosage when all adverse reactions have resolved and no earlier than 12 hours after interruption of the infusion, refer to the SmPC for full details. **Special precautions for storage:** Store BLINCYTO and IV Solution Stabilizer vials in the original package refrigerated at 2°C to 8°C and protect from light until time of use. Do not freeze. BLINCYTO and IV Solution Stabilizer vials may be stored

for a maximum of 8 hours at room temperature [23°C to 27°C] in the original carton to protect from light. **Special precautions for disposal and other handling:** 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), refer to the SmPC for more details**.** ..**Legal Category:** POM, **Administrative information:** date of PI: June 2024, **Marketing authorization holder**: Amgen Inc. One Amgen Center Drive, Thousand Oaks, California 91320-1799, USA. **Registration No**.: 12803-14496-1. **Local representative name and address in UAE**: Pharmatrade. Sky Tower Bldg., 4th floor, Reem Island, Abu Dhabi, UAE. P.O. Box: 71437. Tel: +97125133800 Fax: +97126222083

Any suspected adverse reactions should be reported immediately to Pharmatrade and/Amgen in accordance with local spontaneous reporting requirements. Amgen Global Fax: 0044 2071361046 or send to AGS mailbox: svc-ags-in-uk@amgen.com and Safety-MEA@amgen.com
For any questions or additional information please contact Amgen Medical Information:medinfo-MEA@amgen.com