BLINCYTO®
(blinatumomab)

INTERVENE EARLIER FOR ALL THAT'S AHEAD

FIRST AND ONLY APPROVED IMMUNOTHERAPY FOR MRD+ B-ALL PATIENTS

78% of MRD+ ALL patients achieved a complete MRD response after cycle 1[1,2]

Ph-negative complete MRD responders can achieve **longer Relapse-Free Survival and Overall Survival** than MRD non-responders:

- Median Relapse-Free Survival: 23.6 months (P=0.002)[2]
- Median Overall Survival: 38.9 months (P=0.002)[2]

Generally manageable safety profile[1,2]

ALL=acute lymphoblastic leukemia; B-ALL=B-precursor acute lymphoblastic leukemia; MRD=minimal residual disease.

References: 1. BLINCYTO®(blinatumomab) Full Prescribing Information. January 2023. **2.** Gökbuget N, et al. Blood 2018;131(14):1522-1531.

BLINCYTO® (blinatumomab) Abbreviated Prescribing Information
BLINCYTO® powder for concentrate and solution for solution for infusion 35 mcg/vial

INDICATIONS BLINCYTO is indicated as monotherapy for the treatment of adults with CD19 positive relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL). Patients with Philadelphia chromosome positive B-precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs)and have no alternative treatment options. BLINCYTO is indicated as monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residualdisease (MRD) greater than or equal to 0.1%. BLINCYTO is indicated as monotherapy for the treatment of paediatric patients aged 1 year or older withPhiladelphia chromosome negative CD19 positive B-precursor ALL which is refractory or in relapse afterreceiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation. BLINCYTO is indicated as monotherapy for the treatment of paediatric patients aged 1 year or older withhigh-risk first relapsed Philadelphia chromosome negative CD19 positive B-precursor ALL as part of the consolidation therapy. **DOSAGE AND ADMINISTRATION** For the treatment of relapsed or refractory B-precursor ALL, hospitalisation is recommended for initiationat a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle. For the treatment of Philadelphia chromosome negative MRD positive B-precursor ALL, hospitalisation is recommended at a minimum for the first 3 days of the first cycle and the first 2 days of subsequent cycles.For paediatric patients with high-risk first relapsed B-precursor ALL, hospitalisation is recommended at aminimum for the first 3 days of the cycle. In patients with a history or presence of clinically relevant central nervous system (CNS) pathology, hospitalisation is recommended at a minimum for the first 14 days of the first cycle. In the second cycle, hospitalisation is recommended at a minimum for 2 days,and clinical judgment should be based on tolerance to BLINCYTO in the first cycle. BLINCYTO infusion bags should be prepared to infuse over 24 hours, 48 hours, 72 hours, or 96 hours. See Prescribing Information for details. Posology: *Relapsed or refractory B-precursor ALL* Patients with relapsed or refractory B-precursor ALL, may receive 2 cycles of treatment. A single cycle oftreatment is 28 days (4 weeks) of continuous infusion. Each cycle of treatment is separated by a 14 day (2 week) treatment-free interval. Patients who have achieved complete remission (CR/CRh*) after 2 treatment cycles may receive up to 3 additional cycles of BLINCYTO consolidation treatment, based onan individual benefits-risks assessment. Recommended daily dose is 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). See Prescribing Information for details. *High-risk first relapsed B-precursor ALL* Paediatric patients with high-risk first relapsed B-precursor ALL may receive 1 cycle of BLINCYTOtreatment after induction and 2 blocks of consolidation chemotherapy. A single cycle of treatment is 28 days (4 weeks) of continuous infusion. See Prescribing Information for the recommended daily doseby patient weight for paediatric patients. *Premedication and additional medication recommendations:* In adult patients, dexamethasone 20 mg intravenous should be administered 1 hour prior to initiation of each cycle of BLINCYTO therapy. In paediatric patients, dexamethasone 10 mg/m^2 (not to exceed 20 mg) should be administered orally or intravenously 6 to 12 hours prior to the start of BLINCYTO (cycle 1, day 1). This should be followed by dexamethasone 5 mg/m^2 orally or intravenously within 30 minutes prior to the start of BLINCYTO (cycle1, day 1). *MRD positive B-precursor ALL* When considering the use of BLINCYTO as a treatment for Philadelphia chromosome negative MRD positive B-precursor ALL, quantifiable MRD should be confirmed in a validated assay withminimum sensitivity of 10^{-4}. Patients may receive 1 cycle of induction treatment followed by up to 3 additional cycles of BLINCYTO consolidation treatment. A single cycle of treatment of BLINCYTO induction or consolidation is 28 days (4 weeks) of continuous intravenous infusion followed by a 14 day(2 week) treatment-free interval (total 42 days). *Premedication and additional medication recommendations:* Prednisone 100 mg intravenously or equivalent (e.g. dexamethasone 16 mg) should be administered 1 hour prior to initiation of each cycle ofBLINCYTO therapy. Anti-pyretic use (e.g. paracetamol) is recommended to reduce pyrexia during the first 48 hours of eachtreatment cycle. Intrathecal chemotherapy prophylaxis is recommended before and during BLINCYTOtherapy to prevent central nervous system ALL relapse. *Dosage Adjustments:* If the interruption of treatment after an adverse event is no longer than 7 days, continue the same cycle toa 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. If the toxicity takes more than 14 days to resolve, discontinue BLINCYTO permanently, except if described differently in the Prescribing Information. *Method of administration:* Administer BLINCYTO as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump over a period of up to 96 hours. The pump should be programmable, lockable, non- elastomeric, and have an alarm. The starting volume (270 mL) is more than the volume administered to the patient (240 mL) to account for the priming of the intravenous tubing and to ensure that the patient will receive the full dose of BLINCYTO. *Infuse prepared BLINCYTO final infusion 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/hfor a duration of 48 hours, OR Infusion rate of 3.3 mL/h for a duration of 72 hours, OR Infusion rate of 2.5 mL/h for a duration of 96 hours. Administer prepared BLINCYTO final infusion solution using intravenous tubing that contains a sterile, non-pyrogenic, low protein-binding 0.2 micrometre in-line filter. Important note: Do not flush the BLINCYTO infusion line or intravenous catheter, especially whenchanging 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. The choice of the infusion duration should be made by the treating physician considering the frequency of the infusion bag changes and the weight of the patient. The target therapeutic dose of BLINCYTO delivered does not change. The infusion bag must be changedat least every 96 hours by a healthcare professional for sterility reasons. See Prescribing Information for reconstitution of BLINCYTO and preparation of BLINCYTO Infusion Bag. **CONTRAINDICATIONS** Hypersensitivity to the active substance or to any of the excipients. Breast-feeding. **SPECIAL WARNINGS AND PRECAUTIONS** Neurologic events: Neurologic events including events with a fatal outcome have been observed. Grade 3 or higher (severe or life-threatening) neurologic events following initiation of blinatumomab administration included encephalopathy, seizures, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Infections: In patients receiving blinatumomab, serious infections, including sepsis, pneumonia, bacteraemia, opportunistic infections and catheter site infections have been observed, some of which were life-threatening or fatal. Cytokine releasesyndrome and infusion reactions: Cytokine release syndrome (CRS) which may be life-threatening or fatal has been reported in patients receiving BLINCYTO. Serious adverse events that may be signs and symptoms of CRS included pyrexia, asthenia, headache, hypotension, total bilirubin increased, and nausea; uncommonly, these events led to BLINCYTO discontinuation. Disseminated intravascular coagulation (DIC) and capillary leak syndrome have been commonly associated with CRS. Haemophagocytic histiocytosis/macrophage activation syndrome (MAS) has been uncommonly reported in the setting of CRS. Tumour lysis syndrome: Tumour lysis syndrome (TLS), which may be life- threatening or fatal has been observed in patients receiving BLINCYTO. Appropriate prophylactic measures including aggressive hydration and anti-hyperuricaemic therapy should be used for the prevention and treatment of TLS during BLINCYTO treatment, especially in patients with higher leukocytosis or a high tumour burden. Neutropenia and febrile neutropenia: Neutropenia and febrile neutropenia, including life-threatening cases, have been observed in patients receiving BLINCYTO. Elevated liver enzymes: Treatment with BLINCYTO was associated with transient elevations in liver enzymes. Pancreatitis: Pancreatitis, life-threatening or fatal, has been reported in patients receiving BLINCYTO in clinical trials and the post-marketing setting. High-dose steroid therapy may have contributed, in some cases, to the pancreatitis. Leukoencephalopathy including progressive multifocal leukoencephalopathy: Cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathyhave been observed in patients receiving BLINCYTO, especially in patients with prior treatment with cranial irradiation and anti-leukaemic chemotherapy. Due to the potential for progressive multifocal leukoencephalopathy (PML), patients should be monitored for signs and symptoms. CD19-negative relapse: CD19-negative B-precursor ALL has been reported in relapsed patients receiving BLINCYTO. Particular attention should be given to assessment of CD19 expression at the time of bone marrow testing.Lineage switch from ALL to acute myeloid leukaemia (AML): Lineage switch from ALL to AML has been rarely reported in relapsed patients receiving BLINCYTO, including those with no immunophenotypic and/or cytogenetic abnormalities at initial diagnosis. All relapsed patients should be monitored for presence of AML. Immunisations: Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of BLINCYTO treatment, during treatment, and until recovery of B-lymphocytes to normal ranges following last treatment cycle. Due to the potential depletionof B-cells in newborns following exposure to blinatumomab during pregnancy, newborns should be monitored for B-cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B-cell count has recovered. Contraception: Women of childbearing potential have to use effectivecontraception during and for at least 48 hours, after treatment with BLINCYTO. Medication errors: Medication errors have been observed with BLINCYTO treatment. It is very important that the instructions for preparation (including reconstitution and dilution) and administration are strictly followed to minimise medication errors (including underdose and overdose). **INTERACTIONS** No formal drug interaction studies have been performed. Results from an *in vitro* test in human hepatocytes suggest that blinatumomab did not affect CYP450 enzyme activities. Initiation of BLINCYTO treatment causes transient release of cytokines during the first days of treatment that maysuppress CYP450 enzymes. Patients who are receiving medicinal products that are CYP450 and transporter substrates with a narrow therapeutic index should be monitored for adverse effects (e.g. warfarin) or drug concentrations (e.g. cyclosporine) during this time. The dose of the concomitant medicinal product should be adjusted as needed. **FERTILITY, PREGNANCY AND LACTATION** Pregnancy: There are no data from the use of blinatumomab in pregnant women. Blinatumomab shouldnot be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during and for at least 48 hours aftertreatment with blinatumomab. Breast-feeding: Breast-feeding is contraindicated during and for at least 48 hours after treatment with blinatumomab. Fertility: No studies have been conducted to evaluate theeffects of blinatumomab on fertility. **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES** Blinatumomab has major influence on the ability to drive and use machines. Confusion and disorientation, coordination and balance disorders, risk of seizures and disturbances in consciousness canoccur. Due to the potential for neurologic events, patients receiving blinatumomab should refrain from driving, engaging in hazardous occupations or activities such as driving or operating heavy or potentiallydangerous machinery while blinatumomab is being administered. Patients must be advised that they mayexperience neurologic events. **UNDESIRABLE EFFECTS** The most serious adverse reactions that may occur during blinatumomab treatment include: infections (22.6%), neurologic events (12.2%), neutropenia/febrile neutropenia (9.1%), cytokine release syndrome (2.7%), and tumour lysis syndrome (0.8%). The most common adverse reactions were: pyrexia (70.8%), infections – pathogen unspecified (41.4%), infusion-related reactions (33.4%), headache (32.7%), nausea(23.9%), anaemia (23.3%), thrombocytopenia (21.6%), oedema (21.4%), neutropenia (20.8%), febrile neutropenia (20.4%), diarrhoea (19.7%), vomiting (19.0%), rash (18.0%), hepatic enzyme increased (17.2%), cough (15.0%), bacterial infectious disorders (14.1%), tremor (14.1%), cytokine release syndrome (13.8%), leukopenia (13.8%), constipation (13.5%), decreased immunoglobulins (13.4%), viral infectious disorders (13.3%), hypotension (13.0%), back pain (12.5%), chills (11.7%), abdominal pain (10.6%), tachycardia (10.6%), insomnia (10.4%), pain in extremity (10.1%), and fungal infectious disorders (9.6%). Paediatric population: The most frequently reported serious adverse events were pyrexia (11.4%), febrileneutropenia (11.4%), cytokine release syndrome (5.7%), sepsis (4.3%), device-related infection (4.3%), overdose (4.3%), convulsion (2.9%), respiratory failure (2.9%), hypoxia (2.9%), pneumonia (2.9%), andmulti-organ failure (2.9%). The adverse reactions in BLINCYTO-treated paediatric patients were similarin type to those seen in adult patients. Adverse reactions that were observed more frequently (≥ 10% difference) in the paediatric population compared to the adult population were anaemia, thrombocytopenia, leukopenia, pyrexia, infusion-related reactions, weight increase, and hypertension. Other special populations: Elderly patients with MRD positive ALL treated with BLINCYTO may havean increased risk of hypogammaglobulinaemia compared to younger patients. It is recommended that immunoglobulin levels are monitored in elderly patients during treatment with BLINCYTO. Immunogenicity: In clinical studies of adult ALL patients treated with BLINCYTO, less than 3% testedpositive for anti-blinatumomab antibodies.

Please read the full prescribing information prior to administration and full prescribing information is available upon request. BLINCYTO® is a registered trademark owned or licensed byAmgen Inc., its subsidiaries, or affiliates. Abbreviated Prescribing Information Version: HKBLIPI02

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