BLINCYTO®

WARNING

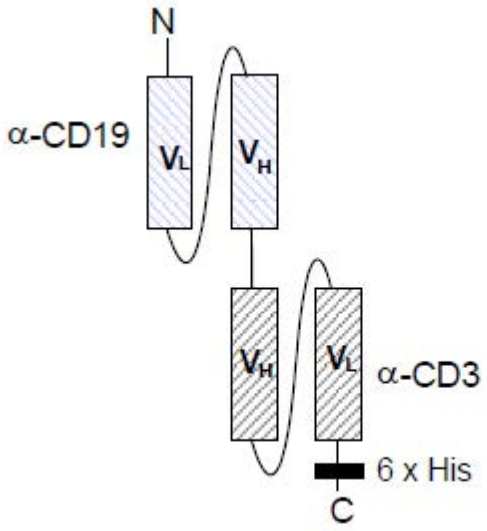
The following have occurred in patients receiving BLINCYTO:

- Cytokine Release Syndrome, which may be life-threatening or fatal
- Neurological toxicities, which may be severe, life-threatening, or fatal
- Reactivation of JC viral infection

Interrupt or discontinue BLINCYTO as recommended if any of these adverse events occur (See Precautions and Dosage and Administration).

NAME OF THE MEDICINE

Blincyto® is the Amgen Inc. trademark for blinatumomab (rch).



CAS number: 853426-35-4

DESCRIPTION

Blinatumomab is a bispecific T cell engager (BiTE®) antibody construct that selectively binds with high affinity to CD19 (expressed on cells of B-lineage origin) and CD3 (expressed on T cells). Using recombinant DNA technology, Blincyto is produced in a well-characterised mammalian cell (Chinese hamster ovary) culture and is purified by a series of steps that include measures to inactivate and remove viruses. It consists of 504 amino acids and has a molecular weight of approximately 54 kilodaltons.

Each single-use vial of Blincyto contains 38.5 micrograms preservative-free blinatumomab, citric acid monohydrate, trehalose dihydrate, lysine hydrochloride, polysorbate 80 and sodium hydroxide. After reconstitution with 3 mL of preservative-free sterile Water for Injections, the resulting total volume of reconstituted solution is 3.1 mL and each mL contains 12.5 micrograms blinatumomab.

Each single use vial of IV solution stabiliser contains citric acid monohydrate, lysine hydrochloride, polysorbate 80, sodium hydroxide (for pH-adjustment) and Water for Injections.

PHARMACOLOGY

Mechanism of action

Blinatumomab is a bispecific T cell engager (BiTE®) antibody construct that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. It activates endogenous T cells by connecting CD3 in the T cell receptor (TCR) complex with CD19 on benign and malignant B cells. The anti-tumour activity of blinatumomab immunotherapy is not dependent on T cells bearing a specific TCR or on peptide antigens presented by cancer cells, but is polyclonal in nature and independent of human leukocyte antigen (HLA) molecules on target cells. Blinatumomab mediates the formation of a cytolytic synapse between the T cell and the B cell, releasing proteolytic enzymes to kill both proliferating and resting target cells. Blinatumomab is associated with transient upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, and results in elimination of CD19+ cells.

Pharmacodynamics

Consistent immune-pharmacodynamic responses were observed in the patients studied. During the continuous intravenous infusion over 4 weeks, the pharmacodynamic response was characterised by T cell activation and initial redistribution, rapid peripheral B cell depletion, and transient cytokine elevation.

Peripheral T cell redistribution (ie, T cell adhesion to blood vessel endothelium and/or transmigration into tissue) occurred after start of Blincyto infusion or dose escalation. T cell counts initially declined within 1 to 2 days and then returned to baseline levels within 7 to 14 days in majority patients. Increase of T cell counts above baseline (T cell expansion) was observed in few patients.

Peripheral B cell counts decreased rapidly to an undetectable level during treatment at doses ≥ 5 micrograms/m^2/day or ≥ 9 micrograms/day in the majority of patients. No recovery of peripheral B cell counts was observed during the 2-week Blincyto-free period between treatment cycles. Incomplete depletion of B cells occurred at doses of 0.5 micrograms/m^2/day and 1.5 micrograms/m^2/day and in a few non-responders at higher doses.

Cytokines including IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, TNF-α, and IFN-γ were measured, and IL-6, IL-10, and IFN-γ were most elevated. Transient elevation of cytokines was observed in the first 2 days following start of Blincyto infusion. The elevated cytokine levels returned to baseline within 24 to 48 hours during the infusion. In subsequent treatment cycles, cytokine elevation occurred in fewer patients with lesser intensity compared to the initial 48 hours of the first treatment cycle.

Pharmacokinetics

The pharmacokinetics of Blincyto appear linear over a dose range from 5 to 90 micrograms/m^2/day (approximately equivalent to 9 to 162 micrograms/day) in adult patients. Following continuous intravenous infusion, the steady state serum concentration (Css) was achieved within a day and remained stable over time. The increase in mean Css values was approximately proportional to the dose in the range tested. At the clinical doses of 9 micrograms/day and 28 micrograms/day for the treatment of relapsed/refractory acute lymphoblastic leukemia (ALL), the mean (SD) Css was 211 (258) pg/mL and 621 (502) pg/mL, respectively.

Distribution

The estimated mean (SD) volume of distribution based on terminal phase (Vz) was 4.52 (2.89) L with continuous intravenous infusion of Blincyto.

Metabolism

The metabolic pathway of Blincyto has not been characterised. Like other protein therapeutics, Blincyto is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination

The estimated mean (SD) systemic clearance with continuous intravenous infusion in patients receiving Blincyto in clinical studies was 2.92 (2.83) L/hour. The mean (SD) half-life was 2.11 (1.42) hours. Negligible amounts of Blincyto were excreted in the urine at the tested clinical doses.

Body weight, Body surface area, Gender, and Age

A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics on Blincyto pharmacokinetics. Results suggest that age (18 to 80 years of age), gender, body weight (44 to 134 kg), and body surface area (1.39 to 2.57 m^2) do not influence the pharmacokinetics of Blincyto.

Special populations

Paediatric

There is limited experience in paediatric patients. The pharmacokinetics of Blincyto was investigated in paediatric patients with relapsed/refractory ALL during a dose escalation/evaluation study. Preliminary pharmacokinetic analysis suggested that mean (SD) steady state concentration (Css) of Blincyto was 620 (305) pg/mL (N=14) in the 7 to 17 years age group, 390 (286) pg/mL (N=12) in the 2 to 6 years age group and 552 (237) pg/mL (N=34) in adults at dose of 15 micrograms/m^2/day under continuous IV infusion. The mean terminal elimination half-lives in paediatric and adult patients were approximately 2 hours.

Use in hepatic impairment

No formal pharmacokinetic studies using Blincyto have been conducted in patients with hepatic impairment. Baseline alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels were used to assess the effect of hepatic impairment on the clearance of Blincyto. Population pharmacokinetic analysis suggested that there was no association between ALT or AST levels and the clearance of blinatumomab.

Use in renal impairment

No formal pharmacokinetic studies of blinatumomab have been conducted in patients with renal impairment. Pharmacokinetic analyses showed an approximately 2-fold difference in mean blinatumomab clearance values between patients with moderate renal dysfunction and normal renal function. Since high inter-subject variability was discerned (CV% up to 95.6%), and clearance values in renal impaired patients were essentially within the range observed in patients with normal renal function, no clinically meaningful impact of renal function on clinical outcomes is expected.

CLINICAL TRIALS

A total of 225 patients aged ≥ 18 years of age with relapsed or refractory B-precursor Acute Lymphoblastic Leukaemia (ALL) were exposed to Blincyto during clinical trials.

In Study 1, the safety and efficacy of Blincyto were evaluated in an open-label, multicentre, dose-escalation study in 36 patients (including 23 patients treated at a dose equivalent to the registrational dose) ≥ 18 years of age with relapsed and/or refractory B-precursor ALL (first or greater relapse, refractory, or relapse after haematopoietic stem cell transplantation [HSCT]). Fifteen out of 36 (41.7%) patients had undergone allogeneic

haematopoietic stem cell transplantation (HSCT) prior to receiving Blincyto. The complete remission/complete remission with partial haematological recovery (CR/CRh*) rate was 69.4% [25 out of 36 patients (95% CI: 51.9% - 83.7%): 15 (41.7%; 95% CI: 25.5% - 59.2%) CR; 10 (27.8%; 95% CI: 14.2% - 45.2%) CRh*]. Twenty-two out of 25 (88%) patients with haematologic CR also had Minimal Residual Disease (MRD) responses (defined as MRD by PCR< 1 x 10^{-4}). The median duration of remission was 8.9 months, and the median relapse-free survival (RFS) was 7.6 months. The median overall survival (OS) was 9.8 months.

In Study 2, the safety and efficacy of Blincyto were evaluated in an open-label, multicentre, single-arm study. Eligible patients were ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-precursor ALL (relapsed with first remission duration of ≤12 months in first salvage or relapsed or refractory after first salvage therapy or relapsed within 12 months of allogeneic HSCT, and had ≥ 10% blasts in bone marrow).

Blincyto was administered as a continuous intravenous infusion. In the first cycle, the initial dose was 9 micrograms/day for week 1, then 28 micrograms/day for the remaining 3 weeks. The target dose of 28 micrograms/day was administered in cycle 2 and subsequent cycles starting on day 1 of each cycle. Dose adjustment was possible in case of adverse events. The treated population included 189 patients who received at least 1 infusion of Blincyto; the median number of treatment cycles was 2 (range: 1 to 5). Patients who responded to Blincyto but later relapsed had the option to be retreated with Blincyto. Among treated patients, the median age was 39 years (range: 18 to 79 years), 64 out of 189 (33.9%) had undergone HSCT prior to receiving Blincyto and 32 out of 189 (16.9%) had received more than 2 prior salvage therapies.

The primary endpoint was the CR/CRh* rate within 2 cycles of treatment with Blincyto. Eighty-one out of 189 (42.9%) patients achieved CR/CRh* within the first 2 treatment cycles with the majority of responses (64 out of 81) occurring within cycle 1 of treatment (see Table 1 and Figure 1 for efficacy results). Four patients achieved CR during subsequent cycles, resulting in a cumulative CR rate of 35.4% (67 out of 189; 95% CI: 28.6% - 42.7%). Thirty-two out of 189 (16.9%) patients underwent allogeneic HSCT in CR/CRh* induced with Blincyto.

Table 1. Efficacy results in patients ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-precursor Acute Lymphoblastic Leukaemia (ALL) (Study 2)

	n (%) N =189	95% CI
Complete remission (CR)[1]/Complete remission with partial haematological recovery (CRh*)[2]	81 (42.9%)	[35.7% – 50.2%]
CR	63 (33.3%)	[26.7% – 40.5%]
CRh*	18 (9.5%)	[5.7% – 14.6%]
Blast free hypoplastic or aplastic bone marrow[3]	17 (9%)	[5.3% – 14.0%]
Partial remission[4]	5 (2.6%)	[0.9% – 6.1%]
Relapse-free survival (RFS) for CR/CRh*	5.9 months	[4.8 to 8.3 months]
Overall survival	6.1 months	[4.2 to 7.5 months]

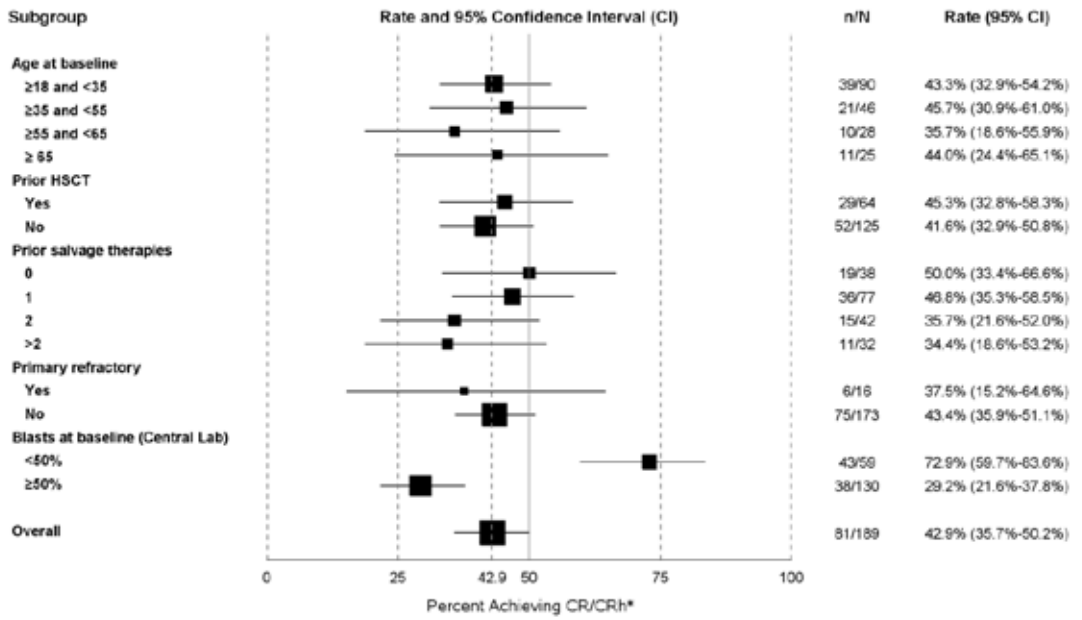
1. CR was defined as £ 5% of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets > 100,000/mL and absolute neutrophil counts [ANC] > 1,000/mL).
2. CRh* was defined as £ 5% of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/mL and ANC > 500/mL).
3. Blast free hypoplastic or aplastic bone marrow was defined as bone marrow blasts £ 5%, no evidence of disease, insufficient recovery of peripheral counts: platelets ≤ 50,000/µL and/or ANC ≤ 500/µL
4. Partial remission was defined as bone marrow blasts 6% to 25% with at least a 50% reduction from baseline

Patients with prior allogeneic HSCT had similar response rates to those without prior HSCT, older patients had similar response rates to younger patients, and no substantial difference was observed in remission rates based on the number of lines of prior salvage treatment. See Figure 1.

To further assess survival, a prespecified landmark analysis comparing responders and non-responders in week 5 of cycles 1 and 2 was conducted. The median overall survival was 11.2 months (95% CI: 7.8 months to not estimable) among patients who achieved CR/CRh* (N = 60) and 3.0 months (95% CI: 2.4 to 4 months) among non-responders (N = 101) in the cycle 1 analysis. The median overall survival was 9.9 months (95% CI: 6.8 months to not estimable) among patients who achieved CR/CRh* (N = 79), and 2.7 months (95% CI: 1.6 to 4.5 months) among nonresponders (N = 50) in the cycle 2 analysis.

In a prespecified exploratory analysis, 60 out of 73 MRD evaluable patients with CR/CRh* (82.2%) also had a MRD response (defined as MRD by PCR < 1 x 10^{-4}).

Figure 1. CR/CRh* Rate During the First Two Cycles by Subgroup (Study 2)



n = number of patients who achieved CR or CRh* in the first two cycles of treatment in the specified group
N = total number of patients in the specified group

In Study 3, Blincyto was evaluated in a confirmatory, multicentre, single-arm study in 116 patients ≥ 18 years of age with MRD including 5 patients (4.3%) with Philadelphia positive ALL. The primary endpoint was the proportion of patients who achieved complete MRD response defined by absence of MRD after one cycle of Blincyto treatment. The percentage of patients who achieved complete MRD response after one cycle of treatment was 77.9% (95% CI: 69.1% - 85.1%).

Study 4 was an open-label, multicentre, single-arm study to establish the safety, efficacy and tolerability of Blincyto in 21 adult patients (≥ 18 years old) with MRD (defined as MRD by PCR ≥ 1 x 10^{-4}) following established induction/consolidation therapy of B-precursor ALL. Patients received blinatumomab doses of 15 µg/m^2/day; non-responders were escalated to 30 µg/m^2/day. The primary endpoint was the MRD response rate, which was defined by the incidence of MRD negativity within 4 cycles of treatment with blinatumomab. MRD response was observed in 80% (16/20) of evaluable patients in the full analysis set, with all MRD responses having been observed within cycle 1.

A pooled analysis of multicentre, historical data (Study 5) on adult relapsed or refractory ALL patients (n = 694 with available CR data; n = 1,112 with available OS data) was performed to provide a summary of key clinical outcomes among patients who receive salvage therapy. The CR definition included patients who experienced complete bone marrow recovery with full peripheral blood count recovery as well as some patients at some centres with partial peripheral blood count recovery. The historical data included relapsed or refractory ALL patients who relapsed within 12 months of initial treatment, were refractory to prior treatment(s), relapsed within 12 months of allogeneic HSCT, or were in second or later salvage treatment. Among these patients, the CR rate, adjusted to the patient profile in Study 2 was 23.8% (95% CI: 19.8% - 27.5%) and median OS was 3.3 months (95% CI: 2.8 to 3.6 months).

The approval for the use of Blincyto in adults with ALL is based upon phase II non-randomised evidence. The results of a randomised, active-controlled phase III study of efficacy and safety for this indication are awaited.

Paediatric population

The safety and efficacy of Blincyto have not yet been established in paediatric patients. Do not use the recommended adult fixed dose in paediatric patients.

INDICATIONS

Blincyto is indicated for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL).

CONTRAINDICATIONS

Blincyto is contraindicated in patients with known hypersensitivity to CHO-cell derived proteins, blinatumomab or any of the excipients (see DESCRIPTION).

PRECAUTIONS

Neurologic Events

Neurologic events have been observed in patients receiving Blincyto. Grade 3 or higher (severe or life-threatening) neurologic events following initiation of Blincyto administration included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. The median time to onset of a neurologic event was 9 days, and the majority of events resolved and infrequently led to Blincyto treatment discontinuation. Some events were reported with a fatal outcome.

There is limited experience with Blincyto in patients with a history of neurologic events. Patients receiving Blincyto should be clinically monitored for signs and symptoms of neurologic events. Management of these signs and symptoms may require either temporary interruption or discontinuation of Blincyto (see DOSAGE AND ADMINISTRATION).

Infections

Patients with ALL are immunocompromised and consequently at increased risk for serious infections. In patients receiving Blincyto, serious infections, including sepsis, pneumonia, bacteraemia, opportunistic infections, and catheter site infections have been observed, some of which were life-threatening or fatal. Patients with Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 experienced a higher incidence of serious infections compared to patients with ECOG performance status of < 2. There is limited experience with Blincyto in patients with an active uncontrolled infection.

Monitor patients for signs and symptoms of infection and treat appropriately. Management of infections may require either temporary interruption or discontinuation of Blincyto (see DOSAGE AND ADMINISTRATION).

Blincyto should be prepared by personnel appropriately trained in aseptic preparation of oncology drugs. Aseptic technique must be strictly observed when preparing the solution for infusion and when performing routine catheter care (see DOSAGE AND ADMINISTRATION, Reconstitution and Preparation of Solution for Infusion).

Cytokine Release Syndrome

Cytokine Release Syndrome (CRS) which may be life-threatening or fatal has been reported in patients receiving Blincyto (Adverse Events).

Serious adverse events that may be associated with CRS included pyrexia, asthenia, headache, hypotension, total bilirubin increased, and nausea; these events infrequently led to Blincyto discontinuation. In some cases, disseminated intravascular coagulation, capillary leak syndrome, and haemophagocytic lymphohistiocytosis/macrophage

activation syndrome have been reported in the setting of CRS. Patients should be closely monitored for signs or symptoms of these events.

Management of these events may require either temporary interruption or discontinuation of Blincyto (see DOSAGE AND ADMINISTRATION).

Infusion Reactions

Infusion reactions may be clinically indistinguishable from manifestations of CRS.

Patients should be observed closely for infusion reactions, especially during the first infusion of the first cycle and treated appropriately. Management of infusion reactions may require either temporary interruption or discontinuation of Blincyto (see DOSAGE AND ADMINISTRATION).

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 hydration should be used for the prevention of TLS during Blincyto treatment. Patients should be closely monitored for signs or symptoms of TLS. Management of these events may require either temporary interruption or discontinuation of Blincyto (see DOSAGE AND ADMINISTRATION).

Neutropenia and Febrile Neutropenia

Neutropenia and febrile neutropenia, including life threatening cases, have been observed in patients receiving Blincyto. Monitor laboratory parameters (including, but not limited to white blood cell count and absolute neutrophil count) during Blincyto infusion and treat appropriately.

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) (see DOSAGE AND ADMINISTRATION).

Elevated Liver Enzymes

Treatment with Blincyto was associated with transient elevations in liver enzymes. The majority of the events were observed within the first week of Blincyto initiation and did not require interruption or discontinuation of Blincyto.

Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during Blincyto treatment (see DOSAGE AND ADMINISTRATION, Preparation and Administration).

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 anti-leukaemic chemotherapy (including systemic high dose methotrexate or intrathecal cytarabine). The clinical significance of these imaging changes is unknown.

Effects on Fertility

No studies have been conducted to evaluate the effects of Blincyto on fertility. There were no effects on male or female mouse reproductive organs in 13-week toxicity studies with the murine surrogate molecule.

Use in Pregnancy

Pregnancy Category: C

The safety and efficacy of blinatumomab in pregnant women has not been established. In a developmental toxicity study conducted in mice using a murine surrogate molecule, there was no indication of maternal toxicity, embryofoetal toxicity, or teratogenicity. The expected depletions of B and T cells were observed in the pregnant mice but haematological effects were not assessed in foetuses.

Treatment of pregnant women with blinatumomab may compromise the immunity of the foetus. Blincyto should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Women of childbearing potential should use contraception during and for at least 24 hours after treatment with Blincyto.

Due to the potential for depletion of B lymphocytes in infants following exposure to BLINCYTO during pregnancy, the infant's B lymphocytes should be monitored before the initiation of live virus vaccination. Live virus vaccines can be administered when the B lymphocytes are within the normal range

Use in Lactation

It is unknown whether blinatumomab or metabolites are excreted in human milk.

A risk to newborns or infants cannot be excluded. Because of the potential for Blincyto to cause adverse effects in infants, nursing should be discontinued during and for at least 24 hours after treatment with Blincyto.

Paediatric Use

The safety and efficacy of Blincyto has not yet been established in paediatric patients. Do not use the recommended adult fixed dose in paediatric patients.

Use in the Elderly

Generally, safety and efficacy were similar between elderly patients (≥ 65 years of age) and patients less than 65 years of age treated with Blincyto. However, elderly patients may be more susceptible to serious neurologic events such as cognitive disorder, encephalopathy, and confusion.

Genotoxicity

No mutagenicity studies have been conducted with blinatumomab; however, blinatumomab is not expected to alter DNA or chromosomes.

Carcinogenicity

No carcinogenicity studies have been conducted with blinatumomab.

Immunogenicity

In clinical studies, 0.9% (2 out of 225) of patients with relapsed or refractory ALL treated with Blincyto tested positive for anti-blinatumomab antibodies; both were neutralising antibodies.

Anti-blinatumomab antibody formation might affect pharmacokinetics of Blincyto. No association was seen between antibody development and development of adverse events.

If formation of anti-blinatumomab antibodies with a clinically significant effect is suspected, contact Amgen's Medical Information line on 1800 803 638 (freecall within Australia) to discuss antibody testing.

The detection of anti-blinatumomab antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to blinatumomab with the incidence of antibodies to other products may be misleading.

Effects on Laboratory Tests

No interactions with laboratory and diagnostic tests have been identified.

Effects on ability to drive and use machines

No studies on effects of Blincyto on the ability to drive and use machines have been performed. However, due to the potential for neurologic events, patients receiving Blincyto should refrain from driving, engaging in hazardous occupations or activities such as driving or operating heavy or potentially dangerous machinery while Blincyto is being administered. Patients should be advised that they may experience neurologic events.

INTERACTIONS WITH OTHER MEDICINES

No formal drug interaction studies have been conducted with Blincyto. Blincyto is not expected to affect CYP450 enzyme activities.

Transient elevation of cytokines may affect CYP450 enzyme activities. Based on physiologically based pharmacokinetic modelling, the effect of transient cytokine elevation on activities of CYP450 enzymes is less than 30%, lasting for less than a week; the effect on exposures to sensitive CYP450 substrates are less than 2-fold. Hence, Blincyto-mediated cytokine elevation appears to have a low potential of clinically meaningful drug interaction.

Immunisation

The safety of immunisation 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 recovery of B lymphocytes to normal range following last cycle of Blincyto.

ADVERSE EFFECTS

The most serious adverse reactions that may occur during Blincyto treatment include: neurologic events, infections, CRS, TLS, and neutropenia/febrile neutropenia.

The most common adverse reactions (occurring in > 20% of patients in a dataset of pooled clinical studies (n = 475)) were: pyrexia, headache, fatigue, nausea, tremor, hypokalaemia, diarrhoea and chills.

Adverse reactions are presented below by system organ class and frequency category. Frequency categories were determined from the crude incidence rate reported for each adverse reaction in a dataset of pooled ongoing and complete clinical studies (n = 475). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**
Infections and infestations	Fungal infections Bacterial infections Viral infections Other pathogen infections	Sepsis Pneumonia	
Blood and lymphatic system disorders	Febrile neutropenia Neutropenia Thrombocytopenia Anaemia Leukopenia Lymphopenia	Leukocytosis	Haemophagocytic histiocytosis
Immune system disorders		Cytokine release syndrome Hypersensitivity	Cytokine storm
Metabolism and nutrition disorders	Hypokalaemia Hyperglycaemia	Tumour lysis syndrome Hypomagnesaemia Hypoalbuminemia	
Psychiatric disorders	Insomnia	Confusion Disorientation	
Nervous system disorders	Tremor Headache Dizziness	Encephalopathy Convulsion Aphasia Paraesthesia Speech disorder Memory impairment Cognitive disorder	
Cardiac disorders		Tachycardia	
Vascular disorders	Hypotension	Capillary leak syndrome	
Respiratory, thoracic and mediastinal disorders	Cough		
Gastrointestinal disorders	Vomiting Abdominal pain Diarrhoea Constipation Nausea		
Hepatobiliary disorders	Increased liver enzymes (including increased alanine aminotransferase, increased aspartate aminotransferase and gamma-glutamyl transferase)	Increased blood bilirubin	
Skin and subcutaneous tissue disorders	Rash		

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)
Musculoskeletal and connective tissue disorders	Back pain Pain in extremity	Arthralgia Bone pain	
General disorders and administration site conditions	Pyrexia Peripheral oedema Fatigue Chills	Chest pain Oedema	
Investigations	Increased weight	Decreased immunoglobulins	
Injury, poisoning and procedural complications	Infusion-related reactions and associated symptoms including wheezing, flushing, face swelling, dyspnoea, hypotension, and hypertension		

Neurologic events

In clinical studies with Blincyto, approximately 50% of patients experienced one or more neurologic adverse reactions (including psychiatric disorders), primarily involving the central nervous system. Serious neurologic adverse reactions were observed in < 20% of patients, of which the most common were encephalopathy, tremor, and confusional state. Fatal encephalopathy has been reported, however, the majority of neurologic events (> 90%) were clinically reversible. The median time to onset of neurologic event was 9 days. For clinical management of neurologic events, see PRECAUTIONS, Neurological Events and DOSAGE AND ADMINISTRATION, Dosage Adjustments.

Infections

Life-threatening or fatal viral, bacterial, and fungal infections have been reported in patients treated with Blincyto. In addition, reactivation of JC and BK viral infections has been observed. Patients with ECOG performance status ≥ 2 experienced a higher incidence of serious infections compared to patients with ECOG performance status of < 2. For clinical management of infections, see PRECAUTIONS, Infections.

Cytokine release syndrome (CRS)

In clinical studies with Blincyto, serious CRS reactions were reported in < 2% of patients with a median time to onset of 2 days. For clinical management of CRS, see PRECAUTIONS, Cytokine Release Syndrome.

Elevated liver enzymes

In clinical studies with Blincyto, approximately 30% of patients reported elevated liver enzymes. Less than 2% of patients experienced serious adverse reactions such as ALT increased, AST increased, and blood bilirubin increased. The median time to onset to the first event was 3 days from the start of Blincyto treatment initiation and did not require interruption or discontinuation of Blincyto. The duration of hepatic adverse reactions has generally been brief and with rapid resolution, often when continuing uninterrupted

treatment with Blincyto. For clinical management of elevated liver enzymes, see PRECAUTIONS, Elevated Liver Enzymes.

Paediatric population

Forty-one paediatric patients (35 patients aged between 2 and 11 years old and 6 patients aged between 12 and 17 years old) with relapsed or refractory ALL have received Blincyto in a dose escalation/evaluation study. The safety results in this study were consistent with the safety profile of Blincyto in adult relapsed or refractory ALL studies.

Post-marketing experience

Not applicable at this time.

DOSAGE AND ADMINISTRATION

Dosage

Blincyto is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump. A single cycle of treatment is 4 weeks of continuous infusion. Each cycle of treatment is separated by a 2-week treatment-free interval. Patients may receive 2 cycles of induction treatment followed by 3 additional cycles of Blincyto consolidation treatment.

Use of Blincyto should be restricted to physicians experienced in the treatment of adult haematological malignancies.

Starting Dose

The recommended initial dose of Blincyto in the first cycle is 9 micrograms/day for week 1 (first 7 days) of treatment.

Subsequent Dose

Increase the dose to 28 micrograms/day starting at week 2 through week 4 of the first cycle. All subsequent cycles should be dosed at 28 micrograms/day throughout the entire 4-week treatment period.

Hospitalisation is recommended at a minimum for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and reinitiation (eg, if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalisation is recommended.

Special Populations

Use in Elderly

No dose adjustment is necessary in elderly patients (≥ 65 years of age).

Use in Paediatrics

The safety and efficacy of Blincyto has not yet been established in paediatric patients.

Renal impairment

No formal pharmacokinetic studies using Blincyto have been conducted in patients with renal impairment. Based on pharmacokinetic analyses, dose adjustment is not necessary in patients with mild to moderate renal dysfunction (see PHARMACOLOGY, Pharmacokinetics).

Hepatic impairment

No formal pharmacokinetic studies using Blincyto have been conducted in patients with hepatic impairment. Since Blincyto is a protein and not metabolised via the hepatic

pathway, the effect of liver dysfunction on drug exposure is not expected and dose adjustment is not necessary (see PHARMACOLOGY, Pharmacokinetics).

Premedication and Additional Medication Recommendations

Premedicate with 20 mg intravenous dexamethasone 1 hour prior to initiation of each cycle of Blincyto therapy.

Intrathecal chemotherapy prophylaxis is recommended before and during Blincyto therapy to prevent central nervous system ALL relapse.

Pre-phase Treatment for Patients with High Tumour Burden

For patients with ≥ 50% leukaemic blasts or > 15,000/µL peripheral blood leukaemic blast counts treat with dexamethasone (not to exceed 24 mg/day).

Dosage Adjustments

Withhold dose if the following occur:

- Grade 3* (severe) neurologic events at 28 micrograms/day dose
- Grade 4* (life-threatening) non-neurologic events

Grade 3* (severe) Neurologic Events: Upon improvement to Grade 1* (mild) or return to baseline, reinitiate treatment at 9 micrograms/day under the supervision of a healthcare professional. The dose may subsequently be increased to 28 micrograms/day. For reinitiation, premedicate with 24 mg dexamethasone with a 4-day taper. As secondary prophylaxis, consider appropriate anticonvulsant medication.

Grade 4* (life-threatening) Non-neurologic Events: Upon improvement to Grade 1* (mild) or return to baseline, reinitiate treatment at 9 micrograms/day or 28 micrograms/day under the supervision of a healthcare professional. If reinitiated at 9 micrograms/day, the dose may be increased to 28 micrograms/day. If treatment interruption is less than 1 week, resume cycle to complete 4 weeks on Blincyto. If treatment interruption is more than 1 week, start a new cycle. A benefit-risk assessment is recommended whether to reinitiate or permanently discontinue Blincyto treatment.

Consider permanent discontinuation if the following occur:

- Grade 4* (life-threatening) neurologic event
- More than one convulsion
- Neurologic event leading to treatment interruption that requires greater than a week to resolve or improve to Grade 1* (mild)
- Grade 3* (severe) neurologic event that occurs at 9 micrograms/day dose leading to treatment interruption

**Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0*

Preparation and Administration

Important Note: Do not flush infusion lines into the patient, as it will cause an inadvertent bolus of drug to be administered. Blincyto should be infused through a dedicated lumen.

The Blincyto solution for infusion must be administered using IV tubing that contains a sterile, nonpyrogenic, low protein-binding 0.2 micron in-line filter.

A therapeutic dose of 9 micrograms/day or 28 micrograms/day should be administered to the patient by infusing a total of 240 mL Blincyto solution for infusion at one of the following constant infusion rates:

- Infusion rate of 10 mL/h for a duration of 24 hours
- Infusion rate of 5 mL/h for a duration of 48 hours
- Infusion rate of 3.3 mL/h for a duration of 72 hours
- Infusion rate of 2.5 mL/h for a duration of 96 hours

Clearly label the prepared IV infusion bag or cassette with the dose, infusion rate and duration of infusion.

At the end of the infusion, any unused Blincyto solution in the IV bag and IV lines should be disposed of in accordance with local requirements.

Change of IV bag or cassette

The IV bag or cassette must be changed at least every 96 hours by a healthcare professional for sterility reasons.

Pump Specifications

The infusion pump used to administer Blincyto solution for infusion should be programmable, lockable and have an alarm. Elastomeric pumps should not be used.

Reconstitution and Preparation of Solution for Infusion

It is very important that the instructions for preparation and administration provided in this section are strictly followed to minimise medication errors (including underdose and overdose) (see PRECAUTIONS).

Aseptic preparation

Blincyto does not contain antimicrobial preservatives, aseptic preparation must therefore be ensured when preparing the infusion. Preparation of Blincyto should be:

- performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products
- prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.

To prevent accidental contamination, prepare Blincyto according to aseptic standards.

Special considerations to support accurate preparation

1. IV Solution Stabiliser is provided with the Blincyto package and is used to coat the prefilled IV bag or cassette prior to addition of reconstituted Blincyto to prevent adhesion of Blincyto to IV bags or cassettes and IV lines. Do not use IV Solution Stabiliser for reconstitution of Blincyto.
2. The entire volume of the reconstituted and diluted Blincyto will be more than the volume administered to the patient (240 mL) to account for the priming of the IV line and to ensure that the patient will receive the full dose of Blincyto.
3. When preparing an IV bag, remove air from IV bag. This is particularly important for use with an ambulatory infusion pump.
4. Use the specific volumes described in the reconstitution and dilution instructions.

Other considerations

- Blincyto is compatible with polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Specific reconstitution and dilution instructions are provided below for each dose and infusion time. Verify the prescribed dose and infusion time of Blincyto and identify the appropriate dosing preparation section listed below. Follow the steps for reconstituting Blincyto and preparing either an IV bag or a cassette.

Gather supplies

NOTE: A Blincyto composite pack includes 1 vial of Blincyto and 1 vial of IV solution stabiliser. Before preparation, ensure you have the following supplies ready.

- 1 package of Blincyto for preparation of:
  - 9 micrograms/day dose infused over 24 hours at a rate of 10 mL/h
  - 9 micrograms/day dose infused over 48 hours at a rate of 5 mL/h
  - 9 micrograms/day dose infused over 72 hours at a rate of 3.3 mL/h
  - 28 micrograms/day dose infused over 24 hours at a rate of 10 mL/h
- 2 packages of Blincyto for preparation of:
  - 9 micrograms/day dose infused over 96 hours at a rate of 2.5 mL/h (note: if using cassettes either 1 or 2 vials may be required)
  - 28 micrograms/day dose infused over 48 hours at a rate of 5 mL/h
- 3 packages of Blincyto for preparation of:
  - 28 micrograms/day dose infused over 72 hours at a rate of 3.3 mL/h
- 4 packages of Blincyto for preparation of:
  - 28 micrograms/day dose infused over 96 hours at a rate of 2.5 mL/h

The extractable amount of blinatumomab per vial is 35 micrograms in a volume of 2.8 mL reconstituted solution.

The following supplies are also required, but **not** included in the package:

- Sterile single-use disposable syringes
- 21 to 23 gauge needle(s) (recommended)
- Preservative-free Sterile Water for Injections
- 250 mL 0.9% sodium chloride IV bag OR a 250 mL cassette
  - **If using IV bags, to minimise the number of aseptic transfers, it is recommended to use a 250 mL-prefilled IV bag. 250 mL prefilled IV bags typically contain overfill with a total volume of 265 to 275 mL. Blincyto dose calculations are based on a starting volume of 265 mL to 275 mL 0.9% sodium sodium chloride.**
  - § Use only polyolefin, PVC non-di-ethylhexylphthalate (non-DEHP), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Polyolefin, PVC non-DEHP, or EVA IV tubing with a sterile, non-pyrogenic, low protein-binding 0.2 micron in-line filter
  - § Ensure that the IV tubing is compatible with the infusion pump

Preparation of Blincyto Solution for Infusion using a Prefilled 250 mL 0.9% Sodium Chloride IV Bag

a) Preparation of Blincyto 9 micrograms/day infused over 24 hours at a rate of 10 mL/h

1. Use a prefilled 250 mL 0.9% Sodium chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% sodium chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.5 mL of IV solution stabiliser to the IV bag. Gently mix the contents of the bag to avoid foaming. Discard remaining IV solution stabiliser vial.
3. Using a 5 mL syringe, reconstitute one vial of Blincyto using 3 mL of preservative-free Sterile Water for Injections. Direct preservative-free Sterile Water for Injections toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do <u>not</u> shake**.
   - **Do not reconstitute Blincyto with IV solution stabiliser.**
   - The addition of preservative-free Sterile Water for Injections to the lyophilised powder results in a total volume of 3.1 mL for a final Blincyto concentration of 12.5 micrograms/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colourless to slightly yellow. **Do <u>not</u> use if solution is cloudy or has precipitated**.
5. Using a 1 mL syringe, aseptically transfer 0.83 mL of reconstituted Blincyto into the IV bag. Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and prime the IV line **only** with the prepared solution for infusion. **Do not prime with 0.9% sodium chloride.**
8. Store at 2°C to 8°C if not used immediately.

b) Preparation of Blincyto 9 micrograms/day infused over 48 hours at a rate of 5 mL/h

1. Use a prefilled 250 mL 0.9% sodium chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% sodium chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.5 mL of IV solution stabiliser to the IV bag. Gently mix the contents of the bag to avoid foaming. Discard remaining IV solution stabiliser vial.
3. Using a 5 mL syringe, reconstitute one vial of Blincyto using 3 mL of preservative-free Sterile Water for Injections. Direct preservative-free Sterile Water for Injections toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do <u>not</u> shake**.
   - **Do <u>not</u> reconstitute Blincyto with IV solution stabiliser.**
   - The addition of preservative-free Sterile Water for Injections to the lyophilised powder results in a total volume of 3.1 mL for a final Blincyto concentration of 12.5 micrograms/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colourless to slightly yellow. **Do <u>not</u> use if solution is cloudy or has precipitated**.

5. Using a 3 mL syringe, aseptically transfer 1.7 mL of reconstituted Blincyto into the IV bag. Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and prime the IV line **only** with the prepared solution for infusion. **Do not prime with 0.9% sodium chloride.**
8. Store at 2°C to 8°C if not used immediately

c) Preparation of Blincyto 9 micrograms/day infused over 72 hours at a rate of 3.3 mL/h

1. Use a prefilled 250 mL 0.9% sodium chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% sodium chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.6 mL of IV solution stabiliser to the IV bag. Gently mix the contents of the bag to avoid foaming. Discard remaining IV solution stabiliser vial.
3. Using a 5 mL syringe, reconstitute one vial of Blincyto using 3 mL of preservative-free Sterile Water for Injections. Direct preservative-free Sterile Water for Injections toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do <u>not</u> shake**.
   - **Do <u>not</u> reconstitute Blincyto with IV solution stabiliser.**
   - The addition of preservative-free Sterile Water for Injections to the lyophilised powder results in a total volume of 3.1 mL for a final Blincyto concentration of 12.5 micrograms/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colourless to slightly yellow. **Do <u>not</u> use if solution is cloudy or has precipitated**.
5. Using a 3 mL syringe, aseptically transfer 2.5 mL of reconstituted Blincyto into the IV bag. Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and prime the IV line **only** with the prepared solution for infusion. **Do not prime with 0.9% sodium chloride.**
8. Store at 2°C to 8°C if not used immediately

d) Preparation of Blincyto 9 micrograms/day infused over 96 hours at a rate of 2.5mL/h

1. Use a prefilled 250 mL 0.9% sodium chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% sodium chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.6 mL of IV solution stabiliser to the IV bag. Gently mix the contents of the bag to avoid foaming. Discard remaining IV solution stabiliser vial.
3. Use two vials of Blincyto. Using a 5 mL syringe, reconstitute each vial of Blincyto using 3 mL of preservative-free Sterile Water for Injections. Direct preservative-free Sterile Water for Injections toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do <u>not</u> shake**.
   - **Do <u>not</u> reconstitute Blincyto with IV solution stabiliser.**

- The addition of preservative-free Sterile Water for Injections to the lyophilised powder results in a total volume of 3.1 mL for a final Blincyto concentration of 12.5 micrograms/mL.

4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colourless to slightly yellow. **Do not use if solution is cloudy or has precipitated**.
5. Using a 3 mL syringe, aseptically transfer 3.3 mL of reconstituted Blincyto into the IV bag (2.0 mL from one vial and the remaining 1.5mL from the second vial). Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and prime the IV line **only** with the prepared solution for infusion. **Do not prime with 0.9% sodium chloride.**
8. Store at 2°C to 8°C if not used immediately

e) Preparation of Blincyto 28 micrograms/day infused over 24 hours at a rate of 10 mL/h

1. Use a prefilled 250 mL 0.9% sodium chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% sodium chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.6 mL of IV solution stabiliser to the IV bag. Gently mix the contents of the bag to avoid foaming. Discard remaining IV solution stabiliser vial.
3. Using a 5 mL syringe, reconstitute one vial of Blincyto using 3 mL of preservative-free Sterile Water for Injections. Direct preservative-free Sterile Water for Injections toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do not shake**.
   - **Do not reconstitute Blincyto with IV solution stabiliser.**
   - The addition of preservative-free Sterile Water for Injections to the lyophilised powder results in a total volume of 3.1 mL for a final Blincyto concentration of 12.5 micrograms/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colourless to slightly yellow. **Do not use if solution is cloudy or has precipitated**.
5. Using a 3 mL syringe, aseptically transfer 2.6 mL of reconstituted Blincyto into the IV bag. Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and prime the IV line **only** with the prepared solution for infusion. **Do not prime with 0.9% sodium chloride.**
8. Store at 2°C to 8°C if not used immediately

f) Preparation of Blincyto 28 micrograms/day infused over 48 hours at a rate of 5 mL/h

1. Use a prefilled 250 mL 0.9% sodium chloride IV bag. 250 mL-pre-filled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% sodium chloride to achieve a starting volume between 265 and 275 mL.

2. Using a 10-mL syringe, aseptically transfer 5.6 mL of IV solution stabiliser to the IV bag. Gently mix the contents of the bag to avoid foaming. Discard remaining IV solution stabiliser vials.
3. Use two vials of Blincyto. Using a 5 mL syringe, reconstitute each vial of Blincyto using 3 mL of preservative-free Sterile Water for Injections. Direct preservative-free Sterile Water for Injections toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do not shake**.
   - **Do not reconstitute Blincyto with IV solution stabiliser.**
   - The addition of preservative-free Sterile Water for Injections to the lyophilised powder results in a total volume of 3.1 mL for a final Blincyto concentration of 12.5 micrograms/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colourless to slightly yellow. **Do not use if solution is cloudy or has precipitated**.
5. Using a 3 mL syringe, aseptically transfer 5.2 mL of reconstituted Blincyto into the IV bag (2.7 mL from one vial and the remaining 2.5 mL from the second vial). Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and prime the IV line **only** with the prepared solution for infusion. **Do not prime with 0.9% sodium chloride.**
8. Store at 2°C to 8°C if not used immediately.

g) Preparation of Blincyto 28 micrograms/day infused over 72 hours at a rate of 3.3 mL/h

1. Use a prefilled 250 mL 0.9% sodium chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% sodium chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.7 mL of IV solution stabiliser to the IV bag. Gently mix the contents of the bag to avoid foaming. Discard remaining IV solution stabiliser vials.
3. Use three vials of Blincyto. Using a 5 mL syringe, reconstitute each vial of Blincyto using 3 mL of preservative-free Sterile Water for Injections. Direct preservative-free Sterile Water for Injections toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do not shake**.
   - **Do not reconstitute Blincyto with IV solution stabiliser.**
   - The addition of preservative-free Sterile Water for Injections to the lyophilised powder results in a total volume of 3.1 mL for a final Blincyto concentration of 12.5 micrograms/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colourless to slightly yellow. **Do not use if solution is cloudy or has precipitated**.
5. Using a 5 mL syringe, aseptically transfer 8 mL of reconstituted Blincyto into the IV bag (3.0 mL from each of the first two vials and the remaining 2.0 mL from the third vial). Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and prime the IV line **only** with the prepared solution for infusion. **Do not prime with 0.9% sodium chloride.**
8. Store at 2°C to 8°C if not used immediately.

h) Preparation of Blincyto 28 micrograms/day infused over 96 hours at a rate of 2.5mL/h

1. Use a prefilled 250 mL 0.9% sodium chloride IV bag. 250 mL-prefilled bags typically contain overfill to a total volume of 265 to 275 mL. If necessary adjust the IV bag volume by adding or removing 0.9% sodium chloride to achieve a starting volume between 265 and 275 mL.
2. Using a 10 mL syringe, aseptically transfer 5.7 mL of IV solution stabiliser to the IV bag. Gently mix the contents of the bag to avoid foaming. Discard remaining IV solution stabiliser vials.
3. Use four vials of Blincyto. Using a 5 mL syringe, reconstitute each vial of Blincyto using 3 mL of preservative-free Sterile Water for Injections. Direct preservative-free Sterile Water for Injections toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do <u>not</u> shake**.
   - **Do not reconstitute Blincyto with IV solution stabiliser.**
   - The addition of preservative-free Sterile Water for Injections to the lyophilised powder results in a total volume of 3.1 mL for a final Blincyto concentration of 12.5 micrograms/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to slightly opalescent, colourless to slightly yellow. **Do <u>not</u> use if solution is cloudy or has precipitated**.
5. Using a 5 mL syringe, aseptically transfer 10.7 mL of reconstituted Blincyto into the IV bag (3.0 mL from each of the first three vials and the remaining 1.7 mL from the fourth vial). Gently mix the contents of the bag to avoid foaming.
6. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
7. Remove air from the IV bag and prime the IV line **only** with the prepared solution for infusion. **Do not prime with 0.9% sodium chloride.**
8. Store at 2°C to 8°C if not used immediately.

i) Preparation of Blincyto Solution for Infusion using a 250 mL cassette

1. Aseptically transfer sterile Sodium Chloride 0.9% Solution for Infusion into the cassette. The volume to transfer should be 250 mL **minus the required volume for the IV solution stabiliser (5 mL) and reconstituted Blincyto (refer Table 2) to be added**. For example, for a cassette that will deliver 9 micrograms/day over 96 hours, load 242 mL Sodium Chloride 0.9% Solution for Infusion into the cassette (250 mL minus 5 mL IV solution stabiliser minus 3 mL reconstituted Blincyto for a total volume of 242 mL). **The final solution volume should equal 250 mL**.
2. Using a 10 mL syringe, aseptically transfer 5 mL of IV solution stabiliser to the cassette. Gently mix the contents of the cassette to avoid foaming. Discard remaining IV solution stabiliser vial.
3. Refer to Table 2 for the expected number of Blincyto vials needed to prepare the required dose of Blincyto for the infusion duration. Using a 5 mL syringe, reconstitute each vial of Blincyto using 3 mL of preservative-free Sterile Water for Injections. Direct preservative-free Sterile Water for Injections toward the side of the vial during reconstitution. Gently swirl contents to avoid excess foaming. **Do <u>not</u> shake**.
   - **Do <u>not</u> reconstitute Blincyto with IV solution stabiliser.**
   - The addition of preservative-free Sterile Water for Injections to the lyophilised powder results in a total volume of 3.1 mL for a final Blincyto concentration of 12.5 micrograms/mL.
4. Visually inspect the reconstituted solution for particulate matter and discoloration during reconstitution and prior to infusion. The resulting solution should be clear to

slightly opalescent, colourless to slightly yellow. **Do not use if solution is cloudy or has precipitated**.

5. Using an appropriate sized syringe, aseptically transfer the required volume (Table 2) of reconstituted Blincyto into the cassette. Gently mix the contents of the cassette to avoid foaming.
   Redraw approximately 10 mL of fluid from the cassette and inject back to ensure no blinatumomab remains in the cassette line. Gently mix again.
6. Remove air from the cassette using a syringe. Under aseptic conditions, attach the IV tubing with the sterile 0.2 micron in-line filter to the cassette.
7. Prime the IV line **only** with the prepared solution for infusion. **Do not prime with 0.9% Sodium Chloride.**
8. Store at 2°C to 8°C if not used immediately.

Table 2. Quantity of Blincyto (blinatumomab) required for 250 mL cassette

Dose per day	**9 mcg**	**9 mcg**	**9 mcg**	**9 mcg**	**28 mcg**	**28 mcg**	**28 mcg**	**28 mcg**
Cassette duration	24 hour	48 hour	72 hour	96 hour	24 hour	48 hour	72 hour	96 hour
Expected Number of Blincyto vials required*	*1*	*1*	*1*	*2*	*1*	*2*	*3*	*4*
Volume of reconstituted Blincyto required for cassette	*0.75 mL*	*1.5 mL*	*2.3 mL*	*3.0 mL*	*2.3 mL*	*4.7 mL*	*7.0 mL*	*9.3 mL*

*Extractable amount per vial is 35 micrograms in a volume of 2.8 mL reconstituted solution.

OVERDOSAGE

Overdoses have been observed including one patient who received 133-fold the recommended therapeutic dose of Blincyto delivered over a short duration. Overdoses resulted in adverse reactions which were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, the infusion should be temporarily interrupted and patients should be monitored. Consider reinitiation of Blincyto at the correct therapeutic dose (see DOSAGE AND ADMINISTRATION).

PRESENTATION AND STORAGE CONDITIONS

Pack size: 1 vial Blincyto and 1 vial IV solution stabiliser for Blincyto supplied in a composite pack.

Each Blincyto pack contains:

- Blincyto supplied in a single-use glass vial as a sterile, preservative-free, white to off-white lyophilised powder (38.5 micrograms/vial) and
- IV solution stabiliser supplied in a 10 mL single-use glass vial as a sterile, preservative-free, colourless to slightly yellow, clear solution. **Do not use the IV solution stabiliser to reconstitute Blincyto.**

It is recommended to store unopened Blincyto and solution stabiliser for Blincyto vials in a refrigerator at 2°C to 8°C in the original carton. Do not freeze. Protect from direct light.

Once removed from the refrigerator, unopened Blincyto and solution stabiliser for Blincyto vials may be stored at or below 25°C for up to 8 hours in the original container (do not freeze).

After reconstitution and dilution

Table 3. Storage Requirements for Reconstituted Blincyto and Prepared IV Bag or cassettes

Maximum storage time of reconstituted Blincyto* solution		Maximum combined storage and infusion time of diluted Blincyto solution in IV bag or cassette	
Room Temperature (Below 25°C**)	**Refrigerated** (2°C to 8°C)	**Room Temperature** (Below 25°C**)	**Refrigerated** 2°C to 8°C
4 hours	24 hours	96 hours***	10 days***

***** While stored, protect reconstituted Blincyto from light.
** Do not freeze
*** If IV bag or cassette containing Blincyto solution for infusion is not administered within the timeframes and temperatures indicated, it must be discarded; it should not be refrigerated again.

The maximum storage time of the prepared IV bag at room temperature should not be longer than 6 hours prior to the start of infusion.

Store and transport the prepared IV bag or cassette containing Blincyto solution at 2°C-8°C (Refrigerate. Do not freeze.)

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 Prescription Medicine

DATE OF FIRST INCLUSION IN THE ARTG

9 November 2015

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