Manual
for
Blinatumomab
Outpatient Administration

S1318

A PHASE II STUDY OF BLINATUMOMAB (NSC-765986) AND POMP (PREDNISONE, VINCRISTINE, METHOTREXATE, 6-MERCAPTOPURINE) FOR PATIENTS ≥ 65 YEARS OF AGE WITH NEWLY DIAGNOSED PHILADELPHIA-CHROMOSOME NEGATIVE (PH-) ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) AND OF DASATINIB (NSC-732517), PREDNISONE AND BLINATUMOMAB FOR PATIENTS ≥ 65 YEARS OF AGE WITH NEWLY DIAGNOSED PHILADELPHIA-CHROMOSOME POSITIVE (PH+) ALL

Provided by SWOG

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BLINATUMOMAB DRUG INFORMATION

Blinatumomab is a fusion protein composed of two single-chain antibodies (scFv), murine anti-CD19 scFv and murine anti-CD3 scFv. Blinatumomab binds to CD3 and recruits and engages T cells for redirected lysis of CD19-positive B cells, including those expressed with B-cell malignancies. T cells are bound by its anti-CD3 moiety, whereas B cells are bound by the anti-CD19 moiety. The subsequent serial lysis of multiple malignant cells by a single blinatumomab-activated T cell closely resembles a natural cytotoxic T cell reaction. Treatment with blinatumomab is associated with a rapid depletion of peripheral B cells, accompanied by T cell activation and a transient increase in cytokines.

ADVERSE EFFECTS

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 269 patients.* Below is the CAEPR for blinatumomab (AMG103).

Version 2.2, February 11, 2015

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 4.0 Term) [n= 486]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
	Blood and lymphatic system disorders - Other (coagulopathy)[2]		***Blood and lymphatic system disorders - Other (coagulopathy)[2] (Gr 2)***

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 4.0 Term) [n= 486]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS contd.)			
		Blood and lymphatic system disorders - Other (lymphadenitis)	
		Blood and lymphatic system disorders - Other (pancytopenia)	
	Disseminated intravascular coagulation[2,3]		***Disseminated intravascular coagulation[2,3] (Gr 2)***
	Febrile neutropenia		***Febrile neutropenia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
		Gastric hemorrhage	
		Gastrointestinal disorders - Other (pneumoperitoneum)	
Nausea			***Nausea (Gr 2)***
		Oral hemorrhage	
		Pancreatitis	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[3]		***Chills[3] (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue[3]			***Fatigue[3] (Gr 2)***
Fever[3]			***Fever[3] (Gr 2)***
	Infusion related reaction		
		Non cardiac chest pain	

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 4.0 Term) [n= 486]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatic function abnormal)[4]		***Hepatobiliary disorders - Other (hepatic function abnormal)[4] (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
	Cytokine release syndrome[3]		
	Immune system disorders - Other (immunodeficiency [immunoglobulin decreased])		***Immune system disorders - Other (immunodeficiency [immunoglobulin decreased]) (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		***Infection[5] (Gr 2)***
INVESTIGATIONS			
		Activated partial thromboplastin time prolonged[2]	
	Alanine aminotransferase increased[4]		***Alanine aminotransferase increased[4] (Gr 2)***
	Alkaline phosphatase increased[4]		***Alkaline phosphatase increased[4] (Gr 2)***
	Aspartate aminotransferase increased[4]		***Aspartate aminotransferase increased[4] (Gr 2)***
	Blood bilirubin increased[4]		***Blood bilirubin increased[4] (Gr 2)***
		Creatinine increased[6]	

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 4.0 Term) [n= 486]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
INVESTIGATIONS (contd.)			
	GGT increased[4]		***GGT increased[4] (Gr 2)***
		Investigations - Other (blood fibrinogen increased)[2]	
	Investigations - Other (C-reactive protein increased)		***Investigations - Other (C-reactive protein increased) (Gr 2)***
		Investigations - Other (fibrin D dimer increased)[2]	
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
	Platelet count decreased[2]		***Platelet count decreased[2] (Gr 2)***
	Weight gain		***Weight gain (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Hyperglycemia		***Hyperglycemia (Gr 2)***
Hypokalemia			***Hypokalemia (Gr 2)***
	Hypomagnesemia		
	Hypophosphatemia		
		Tumor lysis syndrome[7]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Back pain		***Back pain (Gr 2)***
	Bone pain		
	Pain in extremity		***Pain in extremity (Gr 2)***

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 4.0 Term) [n= 486]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
NERVOUS SYSTEM DISORDERS			
	Ataxia[8]		
	Cognitive disturbance[8]		
	Dizziness[8]		***Dizziness[8] (Gr 2)***
		Dysarthria[8]	
	Dysphasia[8]		
	Encephalopathy[8]		
		Facial nerve disorder[8]	
Headache[8]			***Headache[8] (Gr 2)***
		Intracranial hemorrhage	
		Leukoencephalopathy	
	Memory impairment[8]		
	Nervous system disorders - Other (apraxia)		
	Nervous system disorders - Other (cerebellar syndrome)		
		Nervous system disorders - Other[8]	
		Reversible posterior leukoencephalopathy syndrome	
	Seizure[8]		
		Transient ischemic attacks[8]	
Tremor[8]			***Tremor[8] (Gr 2)***

Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 4.0 Term) [n= 486]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
PSYCHIATRIC DISORDERS			
		Agitation[8]	
		Anxiety[8]	
	Confusion[8]		
		Hallucinations[8]	
	Insomnia		***Insomnia (Gr 2)***
		Personality change[8]	
		Psychosis[8]	
RENAL AND URINARY DISORDERS			
	Acute kidney injury[8]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
		Hypoxia	
		Pleural effusion	
		Pneumonitis	
	Respiratory failure		
	Voice alteration[8]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Skin and subcutaneous tissue disorders - Other (rash)[9]		***Skin and subcutaneous tissue disorders - Other (rash)[9] (Gr 2)***
VASCULAR DISORDERS			
		Capillary leak syndrome[3]	
	Flushing[3]		
	Hypertension[3]		***Hypertension[3] (Gr 2)***
	Hypotension[3]		***Hypotension[3] (Gr 2)***
	Thromboembolic event		***Thromboembolic event (Gr 2)***

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Blinatumomab (AMG 103) is known to cause a variety of adverse events associated with coagulopathy which may include: Activated partial thromboplastin time prolonged, Disseminated intravascular coagulation, Fibrinogen decreased, INR increased, Investigations - Other (blood fibrinogen increased), Investigations - Other (fibrin D dimer increased), Investigations - Other (activated partial thromboplastin time shortened), Investigations - Other (antithrombin III decreased), Investigations - Other (coagulation factor XII level decreased), Investigations - Other (coagulation factor XIII level increased), Investigations - Other (haptoglobin decreased), Investigations - Other (protein S decreased), Platelet count decreased, and Thromboembolic events.

[3] Symptoms of cytokine release syndrome (CRS) and/or allergic reaction may include chills, fever, fatigue, flushing, bronchospasm, and hypotension. In some cases, disseminated intravascular coagulation (DIC), capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) have been reported in the setting of CRS

[4] Symptoms of hepatic dysfunction may include alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, blood bilirubin increased, and GGT increased under the INVESTGATIONS SOC.

[5] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[6] Acute kidney injury (acute renal failure) is associated with increased creatinine levels.

[7] Tumor lysis syndrome is defined as a massive overload of potassium, phosphate, uric acid, plus hypocalcemia, potentially causing lethal cardiac arrhythmias and/or renal failure.

[8] Blinatumomab (AMG103) is known to cause a variety of nervous system disorders which may include: Ataxia, dizziness, cognitive disturbance, concentration impairment, depressed level of consciousness, dysphagia, dysarthria, dysesthesia, encephalopathy, facial nerve disorder, headache, memory impairment, paresthesia, peripheral sensory neuropathy, seizure, somnolence, syncope, transient ischemic attacks, tremor, voice alteration, nervous system disorders - allodyniacerebellar syndromedysgraphiaepilepsyfacial palsyhemiparesishypertoniapleocytosispolyneuropathy. Additionally, symptoms of some nervous system disorders are adverse events under the PSYCHIATRIC DISORDERS SOC and may include: Confusion, agitation, anxiety, hallucinations, personality change, and psychosis.

[9] Rash includes rash, rash maculo-papular, erythema, erythematous rash, generalized rash, exanthema, allergic dermatitis, and palmar-plantar erythrodysesthesia syndrome.

Adverse events also reported on blinatumomab (AMG 103) trials but with the relationship to blinatumomab (AMG 103) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Heart failure; Cardiac arrest; Myocardial infarction; Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
CONGENITAL, FAMILIAL AND GENETIC DISORDERS - Congenital, familial and genetic disorders - Other (aplasia)
EAR AND LABYRINTH DISORDERS - Vertigo
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Gait disturbance; General disorders and administration site conditions - Other (thrombosis in device); Hypothermia
INVESTIGATIONS - Investigations - Other (blood lactate dehydrogenase increased); Investigations - Other (hypoproteinemia); Investigations - Other (lipase decreased); Lipase increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Acidosis; Anorexia; Dehydration; Hyperuricemia; Hypoalbuminemia; Metabolism and nutrition disorders - Other (fluid overload)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Generalized muscle weakness
NERVOUS SYSTEM DISORDERS - Somnolence; Syncope
RENAL AND URINARY DISORDERS - Hematuria; Proteinuria; Urinary incontinence
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm[3]; Epistaxis; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Periorbital edema; Pruritus; Skin and subcutaneous tissue disorders - Other (skin irritation)

Note: Blinatumomab (AMG 103) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

DRUG INTERACTIONS

Formal drug interaction studies have not been conducted with blinatumomab.

PREGNANCY AND LACTATION:
Pregnancy Category C. There are no adequate and well-controlled studies of blinatumomab in pregnant women. Based on its mechanism of action, blinatumomab may cause fetal toxicity including B-cell lymphocytopenia when administered to a pregnant woman. In animal embryo-fetal developmental toxicity studies, the murine surrogate molecule crossed the placental barrier but did not cause embryo-fetal toxicity or teratogenicity. No studies of blinatumomab have been conducted in breastfeeding women. Blinatumomab should not be used during breastfeeding.

BLINATUMOMAB FORMULATION AND STABILITY

Blinatumomab and IV solution stabilizer for blinatumomab will be supplied free of charge by Amgen and distributed by NCI/DCTD.

Blinatumomab is available as a **30.3 mcg** preservative-free, white to off-white lyophilized powder for injection in 4 mL single-use vial. The agent is formulated with 2.89 mg citric acid monohydrate, 82.5 mg trehalose dihydrate, 20.1 mg lysine hydrochloride, and 0.55 mg polysorbate 80, pH 7. The stopper of the vial is butyl rubber (IIR), **latex free**.

IV solution stabilizer for blinatumomab (NSC 773150) is **not for reconstitution of blinatumomab;** it is a component of the final intravenous product. The solution is available as a 10 mL single-use vial, preservative-free, clear, colorless-to-slightly yellow liquid solution. Each solution consists of 25 mM citric acid monohydrate, 1.25 M L-lysine hydrochloride, and 0.1% (w/v) polysorbate 80, pH 7. The stopper of the vial is butyl rubber (IIR), latex free.

Store intact vials of blinatumomab and IV solution stabilizer of blinatumomab refrigerated at 2 –8°C (36°-46°F) and protect from light. Shelf life stability studies of the intact vials of blinatumomab and stabilizer solution are ongoing. The stability of the prepared IV solution is 8 days when stored refrigerated at 2° - 8° C. The total storage and administration time must not exceed 8 days. Once at room temperature, discard the IV bag after 96 hours.

BLINATUMOMAB DOSING AND ADMINISTRATION

I. Blinatumomab Dosing Information

General Considerations, Prophylactic Therapy and Pre-Medication

For the prevention of acute reaction, patients must receive dexamethasone 20 mg IV within 1 hour prior to the start of treatment (or re-start of treatment) in each cycle of blinatumomab. For patients with ≥ 5% blasts, dexamethasone 20 mg IV must be given within 1 hour prior to start of blinatumomab infusion at 9 mcg/day on Day 1 and repeat at same dose (dexamethasone 20 mg IV) within 1 hour prior to start of blinatumomab infusion at 28 mcg/day on Day 8.

During treatment with blinatumomab patients must:

1. Receive adequate hydration according to institutional guidelines.

2. Perform a writing test (see Section 18.4) at the time of visits for blinatumumab infusion bag changes or weekly clinical visits. The test will be evaluated immediately by medical staff for evidence of early signs of neurologic toxicity. If changes are noted, patients should be monitored and graded for signs of neurologic toxicity. The writing test samples should be kept in the patient chart; they are not submitted centrally.

3. Avoid non-steroidal anti-inflammatory drugs (NSAIDs) if possible because they are a potential cause of endothelial stress.

4. Be hospitalized per FDA recommendation. If patients have not achieved CR, Cohort 1 (Ph-negative) patients should be hospitalized for the first 9 days of Induction Cycle 1. Similarly, Cohort 2 (Ph-positive) patients with ≥ 5% blasts should be hospitalized for the first 9 days of re-induction Cycle 1. If patients have achieved CR, it is recommended that patients be hospitalized for at least the first 3 days of the first cycle of blinatumomab, and the first 2 days of subsequent cycles.

5. Have blinatumomab bag changed every 24-96 hours.

Note: Home health care for blinatumomab administration and bag changes is acceptable, providing it is in accordance with local policies and procedures and the patient continues to make minimum weekly clinic visits. The Study Chair must be contacted to discuss prior to allowing the patient to receive home health care for blinatumomab.

IMPORTANT NOTE: Please see Clinical Site Management of Out-Patient Treatment Using CTEP-Supplied Blinatumomab and Shipment of Blinatumomab IV Bag from Site/Pharmacy to Patient's Home. All participating investigators must also complete the Outpatient Administration Investigator Statement of Verification, accessible from the SWOG protocol abstract page (www.swog.org), certifying that these materials have been reviewed, that the "Manual for Blinatumomab Outpatient Administration" has been provided to any/all applicable Outpatient Administration Facilities or Organizations that are being utilized at the Investigator's site, and that a communication plan has been established with these same Outpatient Administration Facilities or Organizations.

A. Cohort 1 – Philadelphia Chromosome Negative (Ph-) Patients

1. Registration Step 1 – Induction/Re-Induction – Blinatumomab

Induction

Agent	Dose	Route	Day	Schedule [a]
Blinatumomab [b,c]	9 mcg/day 28 mcg/day	continuous IV continuous IV	1-7 8-28	One Induction cycle One Induction cycle
IT Methotrexate	12 mg	Intrathecal	See Section 7.1a	
Dexamethasone	20 mg	IV	See Section 7.1c	

[a] Note: One cycle = 42 days
[b] For patients with ≥ 5% blasts, blinatumomab will be given at 9 mcg/day for Days 1-7, then increased to 28 mcg/day for Days 8-28.
[c] Patients should be given a blinatumomab medication guide prior to beginning blinatumomab therapy (Patient Information: Medication Guide Blinatumomab)

Blinatumomab Induction/Re-Induction consists of 28 day continuous IV infusion, followed by 14 days of no treatment, for a total of a 42 day cycle.

Response will be assessed at Day 35 (± 2 days) of the Induction cycle. Patients achieving CR or CRi will be registered to Step 2 and receive up to 3 Post-Remission cycles of blinatumomab therapy as outlined in "Registration Step 2 – Post-Remission – Blinatumomab" after completion of the first Induction cycle. Patients may proceed to Step 2 Registration as soon as CR or CRi is documented and the 14 day treatment free period is completed.

Patients not achieving CR or CRi will receive a second cycle of blinatumomab Re-Induction as outlined below, after completion of the first Induction cycle.

Re-Induction

Agent	Dose	Route	Day	Schedule [a]
Blinatumomab [b]	28 mcg/day	continuous IV	1-28	One Re-Induction cycle
IT Methotrexate	12 mg	Intrathecal	See Section 7.1a	
Dexamethasone	20 mg	IV	See Section 7.1c	

[a] Note: One cycle = 42 days
[b] Patients should be given a blinatumomab medication guide prior to beginning blinatumomab therapy (Patient Information: Medication Guide Blinatumomab).

Response will then be assessed again on Day 35 (± 2 days) of the Re-Induction cycle. Patients achieving CR or CRi will be registered to Step 2 and receive up to 3 Post-Remission cycles of blinatumomab therapy as outlined in "Registration Step 2 – Post-Remission – Blinatumomab". Patients may proceed to Step 2 Registration as soon as CR or CRi is documented and the 14 day treatment free period is completed.

Patients not achieving CR or CRi after a second Induction cycle will be removed from protocol therapy.

2. Registration Step 2 – Post-Remission – Blinatumomab

Patients must be registered to Step 2 prior to beginning Post-Remission therapy.

Agent	Dose	Route	Day	Schedule [a]
Blinatumomab [b]	28 mcg/day	continuous IV	1-28	every Post-Remission cycle
IT Methotrexate	12 mg	Intrathecal	See Section 7.1a	
Dexamethasone	20 mg	IV	See Section 7.1c	

[a] Note: One cycle = 42 days
[b] Patients should be given a blinatumomab medication guide prior to beginning blinatumomab therapy (Patient Information: Medication Guide Blinatumomab).

Patients will receive 3 cycles of Post-Remission therapy with blinatumomab. Patients remaining in CR or CRi will proceed to Maintenance as outlined in Section 7.2c. Patients not remaining in CR or CRi will be removed from protocol therapy.

3 Registration Step 3 – Maintenance – POMP Chemotherapy *(does not apply to this manual, please refer to protocol Section 7.2c)*

B. Cohort 2 – Philadelphia Chromosome Positive (Ph+) Patients

1. Registration Step 1 – Induction – Dasatinib/Prednisone *(does not apply to this manual, please refer to protocol Section 7.3a)*

Patients achieving CR or CRi (Day 28 or Day 56) and with continued hematologic remission after Day 84 will then receive up to 3 cycles of post-remission blinatumomab/dasatinib as outlined in "Registration Step 2 – Post-Remission – Blinatumomab/Dasatinib". Patients not achieving CR or CRi by Day 56 will not receive dasatinib on Days 57-84, but will proceed directly to Re-Induction as outlined in "Re-Induction – Blinatumomab". Patients that do not have continued hematologic remission after Day 84 will proceed to Re-Induction as outlined in "Re-Induction – Blinatumomab".

Re-Induction – Blinatumomab

Agent	Dose	Route	Day	Schedule [a]
Blinatumomab [b]	9 mcg/day 28 mcg/day	continuous IV continuous IV	1-7 8-28	Re-Induction Cycle 1 Re-Induction Cycle 1
Blinatumomab	28 mcg/day	continuous IV	1-28	Re-Induction Cycle 2
IT Methotrexate	12 mg	Intrathecal	See Section 7.1a	
Dexamethasone	20 mg	IV	See Section 7.1c	

[a] Note: One cycle = 42 days
[b] Patients should be given a blinatumomab medication guide prior to beginning blinatumomab therapy (Patient Information: Medication Guide Blinatumomab).

Response will be assessed at Day 35 (± 2 days) of Cycle 1. Patients achieving CR or CRi will proceed to blinatumomab/dasatinib therapy as outlined in "Registration Step 2 – Post-Remission – Blinatumomab/Dasatinib". Patients not achieving CR or CRi will receive a second cycle of blinatumomab re-Induction. Response will then be assessed again on Day 35 (± 2 days) of Cycle 2. Patients achieving CR or CRi will proceed to blinatumomab/dasatinib therapy as outlined in "Registration Step 2 – Post-Remission – Blinatumomab/Dasatinib". Patients not achieving CR or CRi will be removed from protocol therapy. Patients may proceed to Step 2 Registration as soon as CR or CRi is documented and the 14 day treatment free period is completed.

2. **Registration Step 2 – Post-Remission** – Blinatumomab/Dasatinib

Patients must be registered to Step 2 prior to beginning Post-Remission therapy.

Agent	Dose	Route	Day	Schedule [a]
Blinatumomab [b]	28 mcg/day	continuous IV	1-28	Post-Remission Cycles 1-3
Dasatinib [c]	70 mg/day	PO	1-42	Post-Remission Cycles 1-3
IT Methotrexate	12 mg	Intrathecal	See Section 7.1a	
Dexamethasone	20 mg	IV	See Section 7.1c	

[a] Note: One cycle = 42 days
[b] Patients should be given a blinatumomab medication guide prior to beginning blinatumomab therapy (Patient Information: Medication Guide Blinatumomab).
[c] Patients should be given a dasatinib handout/wallet card prior to beginning dasatinib therapy (see Section 18.12).

Patients will receive 3 post-remission cycles of blinatumomab/dasatinib therapy. Patients remaining in CR or CRi will proceed to Maintenance as outlined in "Registration Step 3 – Maintenance – Dasatinib/Prednisone". Patients not remaining in CR or CRi will be removed from protocol therapy.

Dasatinib may be taken with or without meals. The dosing time may be adjusted as required (for once daily dosing, recommend skipping doses that are missed by more than 12 hours). If doses are missed for toxicity, they should not be replaced. If vomiting occurs within 30 minutes of intake, that dose may be repeated. Crushing or cutting dasatinib tablets is prohibited.

3. **Registration Step 3 – Maintenance** – Dasatinib/Prednisone *(does not apply to this manual, please refer to protocol Section 7.3d)*

BLINATUMOMAB PREPARATION

Only trained staff may prepare the blinatumomab IV solution. Each site's standard procedure for compounding blinatumomab must be in compliance with the USP < 797 > guidelines (ISO Class 5 or better). Use aseptic technique and prepare the blinatumomab IV solution under a qualified biological safety cabinet.

Blinatumomab must be dispensed in an acceptable IV bag. Acceptable bags include those made of polyolefin/polyethylene, ethylene vinyl acetate (EVA), or PVC non-DEHP.

The final IV solution **MUST** be prepared in the following sequential order (do not deviate from this order; refer to the table below for volume details):

1. **Reconstitute blinatumomab lyophilized powder (30.3 mcg/vial)**
   - Add 3 mL of Sterile Water for Injection (SWFI) to the vial to yield 3.07 mL of blinatumomab at a final concentration of **9.87 mcg/mL.**
   - Rotate the vial to dissolve all powder. Do not shake.
   - The stability of the reconstituted vial is 4 hours at room temperature (22°C – 27°C) or 24 hours refrigerated at 2° – 8°C.
2. **Add the appropriate amount of 0.9% NaCl into the IV bag**
3. **Add the IV solution stabilizer for blinatumomab to the IV bag**
4. **Add the calculated dose (mL) of blinatumomab into the solution in the IV bag**
   - Rotate the IV bag to mix the solution thoroughly. Do not shake. Avoid foaming the solution in the IV bag.
   - Visually inspect for floating particles or discoloration of the IV solution. If floaters or discoloration are present, do not use the prepared solution.

Volume Calculation Table

24-hour IV Bag OUTPATIENT: Infusion rate 10 mL/hr		
	Volume to be prepared	Volume to be infused
24-hour IV bag	1. Add calculated volume of 0.9% NaCl(mL)[1] into approved IV bag 2. Add 5.4 mL IV solution stabilizer for blinatumomab[2] 3. Add blinatumomab calculated dose volume per 270 mL bag(mL)[3] --- 270 mL total volume[4]	240 mL

[1] 0.9% NaCl (mL) = total volume to be prepared (270 mL) – stabilizer solution volume (5.4 mL) – blinatumomab calculated dose volume (mL) per 270 mL bag

[2] stabilizer solution (5.4 mL) = 0.02 x total volume to be prepared (270 mL)

[3] blinatumomab calculated dose volume per 270 mL bag (mL) = 24 hour dose (mcg) ÷ volume to be infused (240 mL) x total volume to be prepared (270 mL) ÷ 9.87 mcg/mL of blinatumomab vial concentration

[4] total volume (270 mL) = Volume to be infused (240 mL) + 30 mL for outpatient IV infusion volume

48-hour IV Bag OUTPATIENT: Infusion rate 5 mL/hr		
	Volume to be prepared	Volume to be infused
48-hour IV bag	1. Add calculated volume of 0.9% NaCl(mL)[1] into approved IV bag 2. Add 5 mL IV solution stabilizer for blinatumomab[2] 3. Add blinatumomab calculated dose volume per 250 mL bag(mL)[3] --- 250 mL total volume[4]	240 mL

[1] 0.9% NaCl (mL) = total volume to be prepared (250 mL) – stabilizer solution volume (5 mL) – blinatumomab calculated dose volume (mL) per 250 mL bag

[2] stabilizer solution (5 mL) = 0.02 x total volume to be prepared (250 mL)

[3] blinatumomab calculated dose volume per 250 mL bag (mL) = 48 hour dose (mcg) ÷ volume to be infused (240 mL) x total volume to be prepared (250 mL) ÷ 9.87 mcg/mL of blinatumomab vial concentration

[4] total volume (250 mL) = Volume to be infused (240 mL) + 10 mL for outpatient IV infusion volume

72-hour IV Bag OUTPATIENT: Infusion rate 3.3 mL/hr		
	Volume to be prepared	Volume to be infused
72-hour IV bag	1. Add calculated volume of 0.9% NaCl(mL)[1] into approved IV bag 2. Add 5 mL IV solution stabilizer for blinatumomab[2] 3. Add blinatumomab calculated dose volume per 250 mL bag(mL)[3] --- 250 mL total volume[4]	238 mL

[1] 0.9% NaCl (mL) = total volume to be prepared (250 mL) – stabilizer solution volume (5 mL) – blinatumomab calculated dose volume (mL) per 250 mL bag

[2] stabilizer solution (5 mL) = 0.02 x total volume to be prepared (250 mL)

[3] blinatumomab calculated dose volume per 250 mL bag (mL) = 72 hour dose (mcg) ÷ volume to be infused (238 mL) x total volume to be prepared (250 mL) ÷ 9.87 mcg/mL of blinatumomab vial concentration

[4] total volume (250 mL) = Volume to be infused (238 mL) + 12 mL for outpatient IV infusion volume

96-Hour IV Bag OUTPATIENT: Infusion rate 2.5 mL/hr		
	Volume to be prepared	Volume to be infused
96-hour IV bag	1. Add calculated volume of 0.9% NaCl(mL)[1] into approved IV bag 2. Add 5 mL IV solution stabilizer for blinatumomab[2] into the normal saline IV bag 3. Add blinatumomab calculated dose volume per 250 mL bag (mL)[3] --- 250 mL total volume[4]	240 mL

[1] 0.9% NaCl (mL) = total volume to be prepared (250 mL) – stabilizer solution volume (5 mL) – blinatumomab calculated dose volume (mL) per 250 mL bag

[2] stabilizer solution (5 mL) = 0.02 x total volume to be prepared (250 mL)

[3] blinatumomab calculated dose volume per 250 mL bag (mL) = 96 hour dose (mcg) ÷ volume to be infused (240 mL) x total volume to be prepared (250 mL) ÷ 9.87 mcg/mL of blinatumomab vial concentration

[4] total volume (250 mL) = Volume to be infused (240 mL) + 10 mL*(will remain in the IV line set) for outpatient IV infusion volume over 96 hours at 2.5mL/hour infusion rate.

Stability of prepared IV blinatumomab solution is 8 days when stored under refrigeration at 2° - 8° C. The total storage and administration time must not exceed 8 days. Once at room temperature, discard the IV bag after 96 hours.

Label the final product with the following information:

- Patient name and number
- Name of the drug
- Dose (mcg/day and volume/day)
- Infusion rate
- Expiration date and time
- CAUTION: NEW DRUG – Limited by United States law to investigational use.
- Bag number

Additional information may be provided on the label in accordance with state, local, and country pharmacy regulations.

GUIDELINES FOR BLINATUMOMAB ADMINISTRATION

IV infusion and infusion set details:

Only **PVC non-DEHP lines with a 0.2 µm inline filter are acceptable**. Prime the IV line with the prepared IV solution prior to administering it to the patient. Do not flush the IV line as it will result in administration of an IV bolus to the patient.

Infusion bags should be changed in accordance with local pharmacy standards for infusion of compounded sterile products. All infusion bags may be changed at least **every 4th day** (not to exceed 96 hours) in the US and in the foreign sites. Shorter time intervals of 24, 48 or 72 hours may also be utilized for convenience of patient scheduling as needed.

For outpatient administration, use FDA approved pumps. Only the exact volume should be administered; any remaining overfill should be discarded appropriately.

IV Bags / IV Infusion Sets:

- IV bags: Polyolefin/polyethylene, ethylene vinyl acetate (EVA) or PVC non-DEHP
- IV Infusion sets: PVC Non-DEHP with 0.2 µm inline filter

Infusion Pump:

- Use programmable pump that is approved by the appropriate regulatory authority for the country in which the subject is undergoing treatment.
- Pump alarm must be visual and auditory.
- Pump must be lockable.
- **Elastomeric pumps are NOT allowed.**
- CADD Infusion pumps are allowed.

Record all infusion interruptions. Technical or logistical interruptions should be minimized. The infusion should be re-started as soon as possible following an interruption. If an interruption is longer than four hours, the re-start of the infusion must take place in the hospital under supervision of the investigator. Monitor patients for potential adverse events as described in the protocol and the Investigator Brochure.

Monitor patients for cytokine release syndrome, tumor lysis syndrome, and infusion reactions. Refer to the protocol for specific recommendations if a reaction occurs. Monitor patients for psychiatric events such as confusion, disorientation, and cognitive attention disturbances. Patients should not drive or operate dangerous machinery while receiving blinatumomab.

CLINICAL SITE MANAGEMENT OF OUT-PATIENT TREATMENT USING CTEP-SUPPLIED BLINATUMOMAB

- PREPARED IV INFUSION BAGS MAY NOT BE CHANGED BY THE STUDY SUBJECT
- PREPARED INFUSION BAGS OR INTACT VIALS MUST NOT BE TRANSPORTED TO ANOTHER LOCATION BY THE STUDY SUBJECT

AGENT PREPARATION AND ADMINISTRATION OPTIONS

- Prepare all out-patient infusion bags at the registering/treating NCTN Network institution. Study subjects should return to the registering/treating institution for all infusion bag changes.

- For study subjects that cannot return to the registering/treating institution every 96-hours for infusion bag exchanges, the next preference would be for **another NCTN Network institution that is participating on the trial and is closer to the subject's home take over** responsibility for the study subject's protocol participation. In such cases, transfer of the subject's protocol registration to another participating investigator and institution should be considered.

- If transferring the subject's protocol registration to another participating investigator and trial site within the NCTN Network is not feasible, use of **a local outpatient infusion center** could be considered.

    - First preference would be for all infusion bags to be prepared by the registering/treating institution and shipped via overnight courier delivery service in a 2^{o} to 8^{o}C pre-qualified shipping container to the local out-patient infusion center.

    - The prepared infusion bags are stored at the local outpatient infusion center. The infusion center would perform each infusion bag change.

    - If the local outpatient infusion center will not administer prepared infusion bags admixed by the registering/treating institution, the registering/treating institution may provide intact vials of blinatumomab to the local outpatient infusion center, with infusion bags prepared and administered by the local outpatient infusion center staff.

    - In either case, the local outpatient infusion center would be managed as a satellite pharmacy of the registering/treating institution (see evaluation criteria below).

    - If physical transport of intact vials of blinatumomab from the registering/treating institution to the local infusion center by registering/treating institution or local infusion center staff is not possible, CTEP will allow shipment of the vials from the registering/treating institution to the local infusion center via overnight courier delivery service in a 2^{o} to 8^{o}C pre-qualified shipping container.

- If an outpatient infusion center is not an option, use of a **home health care service** provider can be considered.

    - The first preference would be for all outpatient infusion bags to be prepared by the registering/treating institution and shipped via overnight courier delivery service in a 2^{o} to 8^{o}C pre-qualified shipping container to the servicing home health care agency.

- The prepared infusion bags are stored by the home health care agency and each individual infusion bag transported to the subject's home by the home health care service nursing staff under refrigerated storage conditions for each infusion bag change.

- If home health care agency will not administer prepared infusion bags admixed by the registering/treating institution, the registering/treating institution may provide intact vials of blinatumomab to the home health care agency, with infusion bags prepared and administered by the home health care agency staff.

- In either case, the home health care agency would be managed as a satellite pharmacy of the registering/treating institution (see evaluation criteria below).

- If physical transport of intact vials of blinatumomab from the registering/treating institution to the home health care agency by registering/treating institution or home health care agency staff is not possible, CTEP will allow shipment of the vials from the registering/treating institution to the home health care agency via overnight courier delivery service in a 2º to 8ºC pre-qualified shipping container.

- If all options above are not feasible, shipping the prepared infusion bags directly to patient's home via overnight courier delivery service for administration by home healthcare agency staff is acceptable.

  - The prepared infusion bags are to be shipped in a 2º to 8ºC pre-qualified shipping container containing one infusion bag per box. Example, if you are making 2 x 48 hour infusion bags, each infusion bag will be shipped in a separate 2º to 8ºC pre-qualified shipping container. The number of infusion bags that may be prepared and shipped is dependent on the duration the shipping container used is qualified to maintain 2º to 8ºC temperature.

  - Patients should NOT open the shipping container upon arrival. Shipping containers are to be stored in a secured area away from reach of children or pets.

  - Shipping containers must only be opened by the home health care service staff at the time of the infusion bag change. Only one shipping container should be opened at a time. If cold-chain management of the prepared infusion bag has been interrupted by opening of the shipping container or storage of the prepared infusion bag in the shipping container exceeds the duration of the qualified time the container will maintain 2º to 8ºC temperature, the infusion bag should not be used.

    The home health care service staff should immediately contact the registering/treating institution site pharmacy as indicated on the shipment form. Within 1 business day, the registering/treating institution site should inform the SWOG Operations office at 210-614-8808 to report such occurrences. SWOG should notify PMB/CTEP at PMBafterhours@mail.nih.gov of all such occurrences of prepared, unusable infusion bags shipped to a patient's home within 1 business day of receiving notification from the registering/treating institution.

  - Form documenting the time of packaging in the shipping container, duration of time the container will maintain 2º to 8ºC temperature and verification that cold-chain management was maintained prior to administration must be included in each shipping container and returned to registering/treating institution for documentation purposes.

  - Home health care service staff is to use GCP guidelines.

EVALUATION OF POTENTIAL SATELLITE PHARMACY SITES

When the registering/treating institution is considering use of a local infusion center or home health care agency as a satellite pharmacy, the following must be assessed by the registering/treating institution in relation to the suitability of the local infusion center or home health care agency:

- Ability to appropriately store (temperature and security) the intact agent vials and/or prepared infusion bags.
- Ability to provide documentation of controlled and monitored temperature storage conditions while the IND agent is in the local infusion center or home health care agency possession.
- Availability of appropriately trained staff to prepare doses in compliance with USP <797> guidelines and the protocol, to label infusion bags according to the protocol instructions and to store agent doses under appropriate controlled temperature conditions.
- For home health care agency services, the ability to transport each prepared dose individually to the subject's home under appropriate controlled storage conditions or the ability to assess and confirm that cold-chain management of prepared infusion bags shipped to the subject's home is maintained prior to administration.
- Availability of appropriately trained staff to administer the prepared doses and perform the infusion bag changes according to the protocol.
- Methods for proper disposal of the waste, empty vials, IV bags, etc. are in place.
- Plan for return of unused intact vials to the registering/treating institution is in place.
- Source documentation to confirm agent administration must be maintained by the local infusion center or home health care agency and must be provided to the registering/treating institution for incorporation into the patient's medical/research records and for audit purposes.
- Plan for handling missed doses is in place.
- Agent accountability must be maintained via use of the NCI Drug Accountability Record Form (DARF). The originating site must keep a Control DARF and the local infusion center or home health care agency would be required to maintain a Satellite DARF if receiving and storing supplies of intact vials or receiving and storing infusion bags prepared by the registering/treating institution. Maintenance of a Satellite DARF is not required by home health care agency staff for prepared infusions bags shipped to the subject's home.
- The DARF must be provided to the registering/treating institution for record keeping purposes and audits.
- Documentation of IRB coverage for the protocol must be maintained. The IRB of record for the site must be informed that the study subject may receive therapy administered by a non-research site (i.e., the local infusion center or home health care agency).

TRAINING FOR ALL PARTICIPATING SITES

The Lead Network Group for the trial must work with participating sites to:

a. Implement a training process for participating NCTN Network sites regarding blinatumomab preparation and administration. Documentation of participating site training must be submitted via RSS as a protocol specific requirement at the time of site activation for participation on the trial

b. Develop a plan for participating NCTN Network sites to assess and train local outpatient infusion centers or home health care agency for patient treatment if required and document training of such sites

c. Have a training manual available for local outpatient infusion centers or home health care agencies on the clinical trial, appropriate agent preparation, handling and administration requirements and appropriate record keeping requirements

d. Create a definitive written communication plan for use between registering/treating institution and the local outpatient infusion centers or home health care agency on an ongoing basis during subject's treatment regimen, including emergency contact information for the registering/treating institution and investigator.

SHIPMENT OF BLINATUMOMAB IV BAG FROM SITE/PHARMACY TO PATIENT'S HOME

To be completed by Site/Pharmacy:

From: (Investigator Name, Address)	**To Patient:** (Patient Initials, Study ID No) _____ ; _____ Patient Initials Study ID Number	**Protocol No.:**
Site Pharmacy contact — — —		

Prepare shipment of IV bag at 2°C to 8°C in validated/pre-qualified insulated shipper as per manufacturer instructions (see shipping container instructions). Please take care to use the applicable instructions for summer or winter package preparation, respectively.

IV Bag number	**Date of packaging** [DD/MMM/YYYY]	**Time of packaging** [hh:mm]	**packed by** (initials)

Please tick the boxes and fill in the information below when preparing the IV bag shipment!

- ☐ **Validated/pre-qualified shipping container duration of time 2°C to 8°C temperature is maintained: _____ hours**
- ☐ **Cooling elements for provided box used according to manufacturer's instruction**

Confirmed by: _____ _____
(print name, signature) (date)

To be completed by Ambulant/Home Care Service Provider:

Shipment box unopened and content intact? **YES** ❒

NO ❒

IF NO, please comment_____

Date and time shipment box opened: _____ _____
(date) (time)

Confirmed by: _____ _____
(print name, signature) Amb. Care Service (date)

Note: **If content is not intact, please do not use IV bag and inform site pharmacy immediately! If time box opened minus time of packaging exceeds the time duration the shipping container maintains 2°C to 8°C, please do not use IV bag and inform site pharmacy immediately!**CONFIDENTIAL

PATIENT INFORMATION: MEDICATION GUIDE BLINATUMOMAB

MEDICATION GUIDE

BLINATUMOMAB
for injection

Read this Medication Guide before you receive BLINATUMOMAB and before each BLINATUMOMAB infusion. There may be new information. This information does not take the place of talking with your study doctor about your medical condition or treatment.

What is the most important information I should know about BLINATUMOMAB?

Call your study doctor or get emergency medical help right away if you get any of the symptoms listed below.

BLINATUMOMAB may cause serious side effects that can be severe, life- threatening, or lead to death, including:

- **Cytokine Release Syndrome (CRS) and Infusion Reactions. Symptoms of CRS and infusion reactions may include:**
  - fever
  - tiredness or weakness
  - dizziness
  - headache
  - low blood pressure
  - nausea
  - vomiting
  - chills
  - face swelling
  - wheezing or trouble breathing
  - skin rash

- **Neurologic problems. Symptoms of neurologic problems may include:**
  - seizures
  - difficulty in speaking or slurred speech
  - loss of consciousness
  - confusion and disorientation
  - loss of balance

Your study doctor will check you for these problems during treatment with BLINATUMOMAB. Your study doctor may temporarily stop or completely stop your treatment with BLINATUMOMAB, if you have severe side effects.

See **"What are the possible side effects of BLINATUMOMAB?"** below for other side effects of BLINATUMOMAB.

What is BLINATUMOMAB?

BLINATUMOMAB is a prescription medicine used to treat a certain type of acute lymphoblastic leukemia (ALL). Acute lymphoblastic leukemia is a cancer of the blood in which a particular kind of white blood cell is growing out of control.

Who should not receive BLINATUMOMAB?

Do not receive BLINATUMOMAB if you are allergic to blinatumomab or to any of the ingredients of BLINATUMOMAB. See the end of this Medication Guide for a complete list of ingredients in BLINATUMOMAB.

What should I tell my study doctor before receiving BLINATUMOMAB?

Before you receive BLINATUMOMAB, tell your study doctor about all of your medical conditions, including if you:

- have a history of neurological problems, such as seizures, confusion, trouble speaking or loss of balance.
- have an infection.
- have ever had an infusion reaction after receiving BLINATUMOMAB or other medications.

Tell your study doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines with you and show it to your study doctor when you get a new medicine.

How will I receive BLINATUMOMAB?

- BLINATUMOMAB will be given to you by intravenous (IV) infusion into your vein by an infusion pump.
- If you are in the Ph negative (Ph-) study group, then:
    - Induction: You will receive BLINATUMOMAB by continuous IV infusion for 4 weeks (28 days), followed by a 2 week break during which you will not be given BLINATUMOMAB. This is one treatment cycle, and this first cycle is considered the "Induction" cycle.
    - Re-Induction: After the 2 week break, your study doctor will conduct a bone marrow exam to see if your leukemia is gone. If it is not gone, you will receive another "Re-Induction" cycle (continuous IV infusion for 4 weeks, followed by a 2 week break), and then you will have another bone marrow exam.
    - Post-Remission: If the leukemia goes away after either the Induction cycle or the Re-Induction cycle, then you will receive 3 more cycles of blinatumomab as "Post-Remission" treatment.
- If you are in the Ph positive (Ph+) study group, then:
    - Induction: You will receive different study drugs (dasatinib by mouth on days 1-84 and prednisone by mouth on days 1-32) for your first treatment ("Induction") cycle (as described in the informed consent document). You will be given a bone marrow exam at 4 weeks and 8 weeks after you start study treatment. If your leukemia is gone after either bone marrow exam you will go on to receive "Post-Remission" therapy.
    - Re-Induction: If your leukemia is not gone, you will receive one cycle of "Re-Induction" therapy, where you will receive BLINATUMOMAB by continuous IV infusion for 4 weeks (28 days), followed by a 2 week break during which you will not be given BLINATUMOMAB. About 1 week after you stop taking, blinatumomab, you will receive a bone marrow exam to see if your leukemia is gone. If your leukemia is not gone then you will receive one more "Re-Induction" cycle (continuous IV infusion of blinatumomab for 4 weeks, followed by a 2 week break), and then you will have another bone marrow exam. If your leukemia is still not gone, then you will not receive any further treatment on this study. If you leukemia is gone after either "Re-Induction" cycle, then you will receive "Post-Remission" treatment.
    - Post-Remission: One "Post-Remission" cycle is 6 weeks, during which you will receive dasatinib by mouth every day. You will also receive BLINATUMOMAB by continuous IV infusion for the first 4 weeks (28 days) of each Post-Remission cycle, followed by a 2 week break during which you will not be given BLINATUMOMAB. You will receive 3 cycles of Post-Remission treatment.

- Most patients will receive BLINATUMOMAB in the hospital for about the first 3 days of the first treatment cycle (that includes blinatumomab treatment) and for the first 2 days of every additional cycle (that includes blinatumomab treatment) to check you for side effects. If you experience side effects, you may also be admitted to the hospital.
- Your study doctor may change your dose of BLINATUMOMAB, delay, or completely stop treatment with BLINATUMOMAB if you have certain side effects.
- Your study doctor will do blood tests during treatment with BLINATUMOMAB to check you for side effects.
- Before you receive BLINATUMOMAB, you will be given a corticosteroid medicine to help reduce infusion reactions.
- It is very important to keep the area around the IV catheter clean to reduce the risk of getting an infection. Your study doctor will show you how to care for your catheter site.
- **Do not change the settings on your infusion pump**, even if there is a problem with your pump or your pump alarm sounds. Any changes to your infusion pump settings may cause a dose that is too high or too low to be given.

CALL YOUR STUDY DOCTOR OR NURSE RIGHT AWAY IF YOU HAVE ANY PROBLEMS WITH YOUR PUMP OR YOUR PUMP ALARM SOUNDS.

What should I avoid while receiving BLINATUMOMAB?
Do not drive, operate heavy machinery, or do other dangerous activities while you are receiving BLINATUMOMAB because BLINATUMOMAB can cause neurological symptoms such as dizziness, seizures, and confusion.

What are the possible side effects of BLINATUMOMAB?

See "What is the most important information I should know?" BLINATUMOMAB may cause serious side effects, including:

- **Infections.** BLINATUMOMAB may cause life-threatening infections that may lead to death. Tell your study doctor right away if you develop an infection.
- **Low white blood cell counts (neutropenia).** Neutropenia is common with BLINATUMOMAB treatment and may sometimes be life-threatening. Low white blood cell counts can increase your risk of infection. Tell your study doctor right away if you get a fever.
- **Abnormal liver blood test.** Your study doctor will do blood tests before you start BLINATUMOMAB and during treatment with BLINATUMOMAB to check your liver.

The most common side effects of BLINATUMOMAB include:

- fever
- headache
- swelling of hands, ankles or feet
- nausea
- constipation
- shaking (tremor)
- rash

Tell your study doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side of effects of BLINATUMOMAB.

How should I store BLINATUMOMAB?

Intravenous bags containing BLINATUMOMAB for infusion will arrive in a special package.

- Do not open the package.
- Do not freeze the package.
- The package containing BLINATUMOMAB will be opened by the home healthcare infusion nurse at the time of the administration of the drug. Only one shipping container should be opened at a time.
- Do not throw away (dispose of) any BLINATUMOMAB in your household trash. Talk with your study doctor about disposal of BLINATUMOMAB and used supplies.

KEEP BLINATUMOMAB AND ALL MEDICINES OUT OF REACH OF CHILDREN.

General information about BLINATUMOMAB

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BLINATUMOMAB for a condition for which it was not prescribed. Do not give BLINATUMOMAB to other people even if they have the same symptoms that you have. It may harm them.

If you would like more information about BLINATUMOMAB, talk with your study doctor. You can ask your pharmacist or study doctor for information about BLINATUMOMAB that is written for health professionals.

For more information, go to www.blinatumomab.com .

What are the ingredients in BLINATUMOMAB?

Active ingredient: blinatumomab
Inactive ingredients: citric acid monohydrate, lysine hydrochloride, polysorbate 80, trehalose dehydrate, and water for injection.