Prescription only

BLINCYTO® Injection 35 micrograms

(blinatumomab, Recombinant protein)

[COMPOSITION]

[Drug Product] 1 vial(134.9685mg) contains

Active Ingredient: blinatumomab (in-house) 38.5 µg

Excipients: Citric Acid Monohydrate, L-Lysine Hydrochloride (stabilizer, 25.55 mg), Polysorbate 80, alpha,alpha-Trehalose Dihydrate (stabilizer, 105.0 mg), Sodium Hydroxide

[IV Solution Stabilizer] 1 vial (10 mL) contains

Citric Acid Monohydrate, L-Lysine Hydrochloride (stabilizer, 2283.8 mg), Polysorbate 80, Sodium Hydroxide, Water for Injection

[APPEARANCE]

Lyophilized vial: White to off white lyophilized cake in a vial for drug product

Reconstitution solution for infusion: Colorless to slightly yellow solution, practically free from particles

IV solution stabilizer: Colorless to slightly yellow solution, practically free from particles in a vial

[INDICATION]

1. MRD-positive B-cell Precursor ALL

THIS DRUG is indicated for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults and children.

2. Relapsed or Refractory B-cell Precursor ALL

THIS DRUG is indicated for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children.

[DOSAGE AND ADMINISTRATION]

1. Dosage

1.1 Treatment of MRD-Positive B-cell Precursor ALL

A. A treatment course consists of 1 cycle of THIS DRUG for induction followed by up to 3 additional cycles for consolidation.

B. A single cycle of treatment of THIS DRUG induction or consolidation consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days).

C. See Table 1 for the recommended dose by patient weight and schedule. Patients weighing 45 kg or more receive a fixed-dose. For patients weighing less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

Table 1. Recommended THIS DRUG Dose and Schedule for the Treatment of MRD-positive B-cell Precursor ALL

Cycle	**Patient Weighing 45 kg or More** ***(Fixed-dose)***	**Patient Weighing Less Than 45 kg** ***(BSA-based dose)***
Induction Cycle 1		
Days 1-28	28 µg/day	15 µg/m^2/day *(not to exceed 28 µg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
Consolidation Cycles 2-4		
Days 1-28	28 µg/day	15 µg/m^2/day *(not to exceed 28 µg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment-free interval

D. Hospitalization is recommended for the first 3 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiations (e.g.,

if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended.

1.2 Treatment of Relapsed or Refractory B-cell Precursor ALL

A. A treatment course consists of up to 2 cycles of THIS DRUG for induction followed by 3 additional cycles for consolidation and up to 4 additional cycles of continued therapy.
B. See Table 2 for the recommended dose by patient weight and schedule. Patients weighing 45 kg or more receive a fixed dose and for patients weighing less than 45 kg, the dose is calculated using the patient's body surface area (BSA).
C. A single cycle of treatment of THIS DRUG induction or consolidation consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days).
D. A single cycle of treatment of THIS DRUG continued therapy consists of 28 days of continuous intravenous infusion followed by a 56-day treatment-free interval (total 84 days).

Table 2. Recommended THIS DRUG Dose and Schedule for the Treatment of Relapsed or Refractory B-cell Precursor ALL

Cycle	**Patient Weighing 45 kg or More** ***(Fixed-dose)***	**Patient Weighing Less Than 45 kg** ***(BSA-based dose)***
Induction Cycle 1		
Days 1-7	9 µg/day	5 µg/m^2/day *(not to exceed 9 µg/day)*
Days 8-28	28 µg/day	15 µg/m^2/day *(not to exceed 28 µg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment-free interval

Cycle	Patient Weighing 45 kg or More *(Fixed-dose)*	Patient Weighing Less Than 45 kg *(BSA-based dose)*
Induction Cycle 2		
Days 1-28	28 µg/day	15 µg/m^2/day *(not to exceed 28 µg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment-free interval
Consolidation Cycles 3-5		
Days 1-28	28 µg/day	15 µg/m^2/day *(not to exceed 28 µg/day)*
Days 29-42	14-day treatment-free interval	14-day treatment free interval
Continued Therapy Cycles 6-9		
Days 1-28	28 µg/day	15 µg/m^2/day *(not to exceed 28 µg/day)*
Days 29-84	56-day treatment-free interval	56-day treatment-free interval

E. Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiation (e.g., if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended.

2. Administration

A. Premedicate with prednisone or equivalent for MRD-positive B-cell Precursor ALL

- For adult patients, premedicate with prednisone 100 mg intravenously or equivalent (e.g., dexamethasone 16 mg) 1 hour prior to the first dose of THIS DRUG in each cycle.
- For pediatric patients, premedicate with 5 mg/m2 of dexamethasone, to a maximum dose of 20 mg prior to the first dose of THIS DRUG in the first cycle and when restarting an infusion after an interruption of 4 or more

hours in the first cycle.

B. Premedicate with dexamethasone for Relapsed or Refractory B-cell Precursor ALL.
   - For adult patients, premedicate with 20 mg of dexamethasone 1 hour prior to the first dose of THIS DRUG of each cycle, prior to a step dose (such as Cycle 1 Day 8), and when restarting an infusion after an interruption of 4 or more hours.
   - For pediatric patients, premedicate with 5 mg/m^2 of dexamethasone, to a maximum dose of 20 mg prior to the first dose of THIS DRUG in the first cycle, prior to a step dose (such as Cycle 1 Day 8), and when restarting an infusion after an interruption of 4 or more hours in the first cycle.

C. Administer THIS DRUG as a continuous intravenous infusion at a constant flow rate using an infusion pump.

D. Prepared THIS DRUG infusion bags should be infused over 24 hours or 48 hours. The choice between 24 hours or 48 hours of the infusion duration should be made by the treating physician considering the frequency of the infusion bag changes.

E. The starting volume (270 mL) is more than the volume administered to the patient (240 mL) to account for the priming of the IV tubing and to ensure that the patient will receive the full dose of THIS DRUG.

F. Infuse THIS DRUG solution according to the instructions on the pharmacy label on the prepared bag at one of the following constant infusion rates:
   - Infusion rate of 10 mL/hour for a duration of 24 hours OR
   - Infusion rate of 5 mL/hour for a duration of 48 hours

3. Dosage Modification for Adverse Reaction

If the interruption after an adverse reaction is no longer than 7 days, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse reaction is longer than 7 days, start a new cycle.

Table 3. Dosage Modification for Adverse Reactions

Toxicity	Grade*	Patients Greater Than or Equal to 45 kg	Patients Less Than 45 kg
Cytokine Release Syndrome (CRS)	Grade 3	• Interrupt THIS DRUG. • Administer dexamethasone 8 mg every 8 hours intravenously or orally for up to 3 days, and taper thereafter over 4 days. • When CRS is resolved, then restart THIS DRUG at 9 µg/day and escalate to 28 µg/day after 7 days if the adverse reaction does not recur.	• Interrupt THIS DRUG. • Administer dexamethasone 5 mg/m^2 (maximum 8 mg) every 8 hours intravenously or orally for up to 3 days and taper thereafter over 4 days. • When CRS resolved, then restart THIS DRUG at 5 µg/m^2/day and escalate to 15 µg/m^2/day after 7 days if the adverse reaction does not recur.
	Grade 4	Discontinue THIS DRUG permanently. Administer dexamethasone as instructed for Grade 3 CRS.	
Neurological Toxicity	Seizure	Discontinue THIS DRUG permanently if more than one seizure occurs.	
	Grade 3	Withhold THIS DRUG until no more than Grade 1 (mild) and for at least 3 days, then restart THIS DRUG at 9 µg/day. Escalate to 28 µg/day after 7 days if the adverse reaction does not recur. If the adverse reaction occurred at 9 µg/day, or if the adverse reaction takes more than 7 days to resolve, discontinue THIS DRUG permanently.	Withhold THIS DRUG until no more than Grade 1 (mild) and for at least 3 days, then restart THIS DRUG at 5 µg/m^2/day. Escalate to 15 µg/m^2/day after 7 days if the adverse reaction does not recur. If the adverse reaction occurred at 5 µg/m^2/day, or if the adverse reaction takes more than 7 days to resolve, discontinue THIS DRUG permanently.
	Grade 4	Discontinue THIS DRUG permanently.	

Toxicity	Grade*	Patients Greater Than or Equal to 45 kg	Patients Less Than 45 kg
Other Clinically Relevant Adverse Reactions	Grade 3	Withhold THIS DRUG until no more than Grade 1 (mild), then restart THIS DRUG at 9 µg/day. Escalate to 28 µg/day after 7 days if the adverse reaction does not recur. If the adverse reaction takes more than 14 days to resolve, discontinue THIS DRUG permanently.	Withhold THIS DRUG until no more than Grade 1 (mild), then restart THIS DRUG at 5 µg/m^2/day. Escalate to 15 µg/m^2/day after 7 days if the adverse reaction does not recur. If the adverse reaction takes more than 14 days to resolve, discontinue THIS DRUG permanently.
	Grade 4	Consider discontinuing THIS DRUG permanently.	

* Based on the Common Terminology Criteria for Adverse Event (CTCAE). Grade 3 is severe, and Grade 4 is life-threatening.

[PRECAUTIONS FOR USE]

1. Warnings

A. Cytokine Release Syndrome

Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving THIS DRUG. The median time to onset of CRS was 2 days after the start of infusion and the median time to resolution of CRS was 5 days among cases that resolved. Manifestations of CRS include fever, headache, nausea, asthenia, hypotension, increased ALT, increased AST, increased total bilirubin, and disseminated intravascular coagulation. The manifestations of CRS after treatment with THIS DRUG overlap with those of infusion reactions, capillary leak syndrome, and hemophagocytic histocytosis/macrophage activation syndrome. Using all of these terms to define CRS in clinical trials of THIS DRUG, CRS was reported in 15% of patients with relapsed or refractory ALL and in 7% of patients with MRD-positive ALL.

Monitor patients for signs or symptoms of these events. Advise patients on BLINCYTO to contact their healthcare professional for signs and symptoms associated with CRS. If severe CRS occurs, interrupt THIS DRUG until CRS resolves. Discontinue THIS DRUG permanently if life-threatening CRS occurs. Administer corticosteroids for sever or life-threatening CRS.

B. Neurological Toxicities

In patients with ALL receiving THIS DRUG in clinical studies, neurological toxicities have occurred in approximately 65% of patients. Among patients that experienced a neurologic event, the median time to the first event was within the first 2 weeks of THIS DRUG treatment and the majority of events resolved. The most common (≥ 10%) manifestations of neurological toxicity were headache and tremor; the neurological toxicity profile varied by age group. Grade 3 or higher (severe, life-threatening, or fatal) neurological toxicities following initiation of THIS DRUG administration occurred in approximately 13% of patients and included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Manifestations of neurological toxicity included cranial nerve disorders. The majority of neurologic events resolved following interruption of THIS DRUG, but some resulted in treatment discontinuation.

There is limited experience with THIS DRUG in patients with active ALL in the central nervous system (CNS) or a history of neurologic events. Patients with a history or presence of clinically relevant CNS pathology were excluded from clinical trials.

Monitor patients receiving THIS DRUG for signs and symptoms of neurological toxicities. Advise patients on THIS DRUG to contact their healthcare professional if they develop signs or symptoms of neurological toxicities. Interrupt or discontinue THIS DRUG as recommended

2. Contraindications

THIS DRUG is contraindicated in patients with known hypersensitivity to blinatumomab or to any component of the product formulation.

3. Adverse Reactions

A. Clinical Trials Experience

MRD-positive B-cell Precursor ALL

The safety of THIS DRUG in patients with MRD-positive B-cell precursor ALL was evaluated in two single-arm clinical studies in which 137 patients were treated with THIS DRUG. The median age of the study population was 45 years (range: 18 to 77 years).

The most common adverse reactions (≥ 20%) were pyrexia, infusion related reactions, headache, infections (pathogen unspecified), tremor, and chills. Serious adverse reactions were reported in 61% of patients. The most common serious adverse reactions (≥ 2%) included pyrexia, tremor, encephalopathy, aphasia, lymphopenia, neutropenia, overdose, device related infection, seizure, and staphylococcal infection. Adverse reactions of Grade 3 or higher were reported in 64% of patients. Discontinuation of therapy due to adverse reactions occurred in 17% of patients; neurologic events were the most frequently reported reasons for discontinuation. There were 2 fatal adverse reaction that occurred within 30 days of the end of THIS DRUG treatment (atypical pneumonia and subdural hemorrhage).

Table 4 summarizes the adverse reactions occurring at a ≥ 10% incidence for any grade or ≥ 5% incidence for Grade 3 or higher.

Table 4. Adverse Reactions Occurring at ≥ 10% Incidence for Any Grade or ≥ 5% Incidence for Grade 3 or Higher in THIS DRUG-Treated Patients with MRD-Positive B-cell Precursor ALL

Adverse Reaction	THIS DRUG (N=137)	
	Any Grade* n (%)	Grade ≥ 3* n (%)
Blood and lymphatic system disorders		
Neutropenia[1]	21 (15)	21 (15)
Leukopenia[2]	19 (14)	13 (9)
Thrombocytopenia[3]	14 (10)	8 (6)
Cardiac disorders		
Arrhythmia[4]	17 (12)	3 (2)
General disorders and administration site conditions		
Pyrexia[5]	125 (91)	9 (7)
Chills	39 (28)	0 (0)
Infections and infestations		
Infections - pathogen unspecified	53 (39)	11 (8)
Injury, poisoning and procedural complications		
Infusion related reaction[6]	105 (77)	7 (5)
Investigations		
Decreased immunoglobulins[7]	25 (18)	7 (5)
Weight increased	14 (10)	1 (<1)
Hypertransaminasemia[8]	13 (9)	9 (7)
Musculoskeletal and connective tissue disorders		
Back pain	16 (12)	1 (<1)
Nervous system disorders		
Headache	54 (39)	5 (4)
Tremor[9]	43 (31)	6 (4)
Aphasia	16 (12)	1 (<1)
Dizziness	14 (10)	1 (<1)
Encephalopathy[10]	14 (10)	6 (4)
Psychiatric disorders		
Insomnia[11]	24 (18)	1 (<1)
Respiratory, thoracic and mediastinal disorders		
Cough	18 (13)	0 (0)
Skin and subcutaneous tissue disorders		
Rash[12]	22 (16)	1 (<1)

Adverse Reaction	THIS DRUG (N=137)	
	Any Grade* n (%)	Grade ≥ 3* n (%)
Vascular disorders		
Hypotension	19 (14)	1 (<1)

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

1 Neutropenia includes febrile neutropenia, neutropenia, and neutrophil count decreased

2 Thrombocytopenia includes platelet count decreased and thrombocytopenia

3 Leukopenia includes leukopenia and white blood cell count decreased

4 Arrhythmia includes bradycardia, sinus arrhythmia, sinus bradycardia, sinus tachycardia, tachycardia and ventricular extrasystoles

5 Pyrexia includes body temperature increased and pyrexia

6 Infusion-related reaction is a composite term that includes the term infusion-related reaction and the following events occurring with the first 48 hours of infusion and the event lasted ≤ 2 days: cytokine release syndrome, eye swelling, hypertension, hypotension, myalgia, periorbital edema, pruritus generalized, pyrexia, and rash

7 Decreased immunoglobulins includes blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, hypogammaglobulinemia, hypoglobulinemia, and immunoglobulins decreased

8 Hypertransaminasemia includes alanine aminotransferase increased, aspartate aminotransferase increased, and hepatic enzyme increased

9 Tremor includes essential tremor, intention tremor, and tremor

10 Encephalopathy includes cognitive disorder, depressed level of consciousness, disturbance in attention, encephalopathy, lethargy, leukoencephalopathy, memory impairment, somnolence, and toxic encephalopathy

11 Insomnia includes initial insomnia, insomnia, and terminal insomnia

12 Rash includes dermatitis contact, eczema, erythema, rash, and rash maculopapular

Additional adverse reactions in patients with MRD-positive ALL that did not meet the threshold criteria for inclusion in Table 4 were:

Blood and lymphatic system disorders: anemia

General disorders and administration site conditions: edema peripheral, pain, and chest pain (includes chest pain and musculoskeletal chest pain)

Hepatobiliary disorders: blood bilirubin increased

Immune system disorders: hypersensitivity and cytokine release syndrome

Infections and infestations: viral infectious disorders, bacterial infectious disorders, and fungal infectious disorders

Injury, poisoning and procedural complications: medication error and overdose (includes overdose and accidental overdose)

Investigations: blood alkaline phosphatase increased

Musculoskeletal and connective tissue disorders: pain in extremity and bone pain
Nervous system disorders: seizure (includes seizure and generalized tonic-clonic seizure), speech disorder, and hypoesthesia
Psychiatric disorders: confusional state, disorientation, and depression
Respiratory, thoracic and mediastinal disorders: dyspnea and productive cough
Vascular disorders: hypertension (includes blood pressure increased and hypertension) flushing (includes flushing and hot flush), and capillary leak syndrome

Philadelphia Chromosome-negative Relapsed or Refractory B-cell Precursor ALL
The safety of THIS DRUG was evaluated in a randomized, open-label, active-controlled clinical study (TOWER Study) in which 376 patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL were treated with THIS DRUG (n = 267) or standard of care (SOC) chemotherapy (n = 109). The median age of THIS DRUG-treated patients was 37 years (range: 18 to 80 years), 60% were male, 84% were White, 7% Asian, 2% were Black or African American, 2% were American Indian or Alaska Native, and 5% were Multiple/Other.

The most common adverse reactions (≥ 20%) in the THIS DRUG arm were infections (bacterial and pathogen unspecified), pyrexia, headache, infusion-related reactions, anemia, febrile neutropenia, thrombocytopenia, and neutropenia. Serious adverse reactions were reported in 62% of patients. The most common serious adverse reactions (≥ 2%) included febrile neutropenia, pyrexia, sepsis, pneumonia, overdose, septic shock, CRS, bacterial sepsis, device related infection, and bacteremia. Adverse reactions of Grade 3 or higher were reported in 87% of patients. Discontinuation of therapy due to adverse reactions occurred in 12% of patients treated with THIS DRUG; neurologic events and infections were the most frequently reported reasons for discontinuation of treatment due to an adverse reaction. Fatal adverse events occurred in 16% of patients. The majority of the fatal events were infections.

The adverse reactions occurring at a ≥ 10% incidence for any grade or ≥ 5% incidence for Grade 3 or higher in the THIS DRUG-treated patients in first cycle of therapy are summarized in Table 5.

Table 5. Adverse Reactions Occurring at ≥ 10% Incidence for Any Grade or ≥ 5% Incidence for Grade 3 or Higher in THIS DRUG-treated Patients in First Cycle of Therapy

Adverse Reaction	THIS DRUG (N = 267)		Standard of Care (SOC) Chemotherapy (N = 109)	
	Any Grade* n (%)	Grade ≥ 3* n (%)	Any Grade* n (%)	Grade ≥ 3* n (%)
Blood and lymphatic system disorders				
Neutropenia[1]	84 (31)	76 (28)	67 (61)	61 (56)
Anemia[2]	68 (25)	52 (19)	45 (41)	37 (34)
Thrombocytopenia[3]	57 (21)	47 (18)	42 (39)	40 (37)
Leukopenia[4]	21 (8)	18 (7)	9 (8)	9 (8)
Cardiac disorders				
Arrhythmia[5]	37 (14)	5 (2)	18 (17)	0 (0)
General disorders and administration site conditions				
Pyrexia	147 (55)	15 (6)	43 (39)	4 (4)
Edema[6]	48 (18)	3 (1)	20 (18)	1 (1)
Immune system disorders				
Cytokine release syndrome[7]	37 (14)	8 (3)	0 (0)	0 (0)
Infections and infestations				
Infections - pathogen unspecified	74 (28)	40 (15)	50 (46)	35 (32)
Bacterial infectious disorders	38 (14)	19 (7)	35 (32)	21 (19)
Viral infectious disorders	30 (11)	4 (1)	14 (13)	0 (0)
Fungal infectious disorders	27 (10)	13 (5)	15 (14)	9 (8)
Injury, poisoning and procedural complications				
Infusion-related reaction[8]	79 (30)	9 (3)	9 (8)	1 (1)
Investigations				
Hypertransaminasemia[9]	40 (15)	22 (8)	13 (12)	7 (6)
Nervous system disorders				
Headache	61 (23)	1 (<1)	30 (28)	3 (3)
Skin and subcutaneous tissue disorders				
Rash[10]	31 (12)	2 (1)	21 (19)	0 (0)

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

1 Neutropenia includes agranulocytosis, febrile neutropenia, neutropenia, and neutrophil count decreased

2 Anemia includes anemia and hemoglobin decreased

3 Thrombocytopenia includes platelet count decreased and thrombocytopenia

[4] Leukopenia includes leukopenia and white blood cell count decreased

[5] Arrhythmia includes arrhythmia, atrial fibrillation, atrial flutter, bradycardia, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, and tachycardia

[6] Edema includes face edema, fluid retention, edema, edema peripheral, peripheral swelling, and swelling face

[7] Cytokine release syndrome includes cytokine release syndrome and cytokine storm

[8] Infusion-related reaction is a composite term that includes the term infusion-related reaction and the following events occurring with the first 48 hours of infusion and the event lasted ≤ 2 days: pyrexia, cytokine release syndrome, hypotension, myalgia, acute kidney injury, hypertension, and rash erythematous

[9] Hypertransaminasemia includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased

[10] Rash includes erythema, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash pruritic, skin exfoliation, and toxic skin eruption.

Selected laboratory abnormalities worsening from baseline Grade 0-2 to treatment-related maximal Grade 3-4 in first cycle of therapy are shown in Table 6.

Table 6. Selected Laboratory Abnormalities Worsening from Baseline Grade 0-2 to Treatment-related Maximal Grade 3-4* in First Cycle of Therapy

	THIS DRUG Grade 3 or 4 (%)	**SOC Chemotherapy** Grade 3 or 4 (%)
Hematology		
Decreased lymphocyte count	80	83
Decreased white blood cell count	53	97
Decreased hemoglobin	29	43
Decreased neutrophil count	57	68
Decreased platelet count	47	85
Chemistry		
Increased ALT	11	11
Increased bilirubin	5	4
Increased AST	8	4

* Includes only patients who had both baseline and at least one laboratory measurement during first cycle of therapy available.

Relapsed or Refractory B-cell Precursor ALL

Other important adverse reactions from pooled relapsed or refractory B-cell precursor ALL studies were:

Blood and lymphatic system disorders: lymphadenopathy, hematophagic histiocytosis, and leukocytosis (includes leukocytosis and white blood cell count increased)

General disorders and administration site conditions: chills, chest pain (includes chest discomfort, chest pain, musculoskeletal chest pain, and non-cardiac chest pain), pain, body temperature increased, hyperthermia, and systemic inflammatory response syndrome

Hepatobiliary disorders: hyperbilirubinemia (includes blood bilirubin increased and hyperbilirubinemia)

Immune system disorders: hypersensitivity (includes hypersensitivity, anaphylactic reaction, angioedema, dermatitis allergic, drug eruption, drug hypersensitivity, erythema multiforme, and urticaria)

Injury, poisoning and procedural complications: medication error and overdose (includes overdose, medication error, and accidental overdose)

Investigations: weight increased, decreased immunoglobulins (includes immunoglobulins decreased, blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, and hypogammaglobulinemia), blood alkaline phosphatase increased, and hypertransaminasemia

Metabolism and nutrition disorders: tumor lysis syndrome

Musculoskeletal and connective tissue disorders: back pain, bone pain, and pain in extremity

Nervous system disorders: tremor (resting tremor, intention tremor, essential tremor, and tremor), altered state of consciousness (includes altered state of consciousness, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, stupor, and somnolence), dizziness, memory impairment, seizure (includes seizure and atonic seizure), aphasia, cognitive disorder, speech disorder, hypoesthesia, and encephalopathy and cranial nerve disorders (trigeminal neuralgia, trigeminal nerve disorder, sixth nerve paralysis, cranial nerve disorder, facial nerve disorder, and facial paresis).

Psychiatric disorders: insomnia, disorientation, confusional state, and depression (includes depressed mood, depression, suicidal ideation, and completed suicide)

Respiratory, thoracic and mediastinal disorders: dyspnea (includes acute respiratory failure, dyspnea, dyspnea exertional, respiratory failure, respiratory distress, bronchospasm, bronchial hyperreactivity, tachypnea, and wheezing), cough, and productive cough

Vascular disorders: hypotension (includes blood pressure decreased, hypotension, hypovolemic shock, and circulatory collapse), hypertension (includes blood pressure increased, hypertension, and hypertensive crisis), flushing (includes flushing and hot flush), and capillary leak syndrome

B. Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity.

In clinical studies, less than 2% of patients treated with THIS DRUG tested positive for binding anti-blinatumomab antibodies. Of patients who developed anti-blinatumomab antibodies, 7 out of 9 (78%) had *in vitro* neutralizing activity. Anti-blinatumomab antibody formation may affect pharmacokinetics of THIS DRUG.

C. Postmarketing Experience

The following adverse reactions have been identified during postapproval use of THIS DRUG. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Fatal pancreatitis, has been reported in patients receiving THIS DRUG in combination with dexamethasone.

4. General Cautions

A. Infections

In patients with ALL receiving THIS DRUG in clinical studies, serious infections such as sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site infections were observed in approximately 25% of patients, some of which were life-threatening or fatal. As appropriate, administer prophylactic antibiotics and employ surveillance testing during treatment with THIS DRUG. Monitor patients for signs and symptoms of infection and treat appropriately.

B. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), which may be life-threatening or fatal, has been observed in patients receiving THIS DRUG. Appropriate prophylactic measures, including pretreatment nontoxic cytoreduction and on-treatment hydration, should be used for the prevention of TLS during THIS DRUG treatment. Monitor for signs or symptoms of TLS. Management of these events may require either temporary interruption or discontinuation of THIS DRUG.

C. Neutropenia and Febrile Neutropenia

Neutropenia and febrile neutropenia, including life-threatening cases, have been observed in patients receiving THIS DRUG. Monitor laboratory parameters (including, but not limited to, white blood cell count and absolute neutrophil count) during THIS DRUG'S infusion. Interrupt THIS DRUG if prolonged neutropenia occurs.

D. Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including seizures, patients receiving THIS DRUG are at risk for loss of consciousness. Advise patients to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while THIS DRUG is being administered.

E. Elevated Liver Enzymes

Treatment with THIS DRUG was associated with transient elevations in liver enzymes. In patients with ALL receiving THIS DRUG in clinical studies, the median time to onset of elevated liver enzymes was 3 days.

The majority of these transient elevations in liver enzymes were observed in the setting of CRS. For the events that were observed outside the setting of CRS, the median time to onset was 19 days. Grade 3 or greater elevations in liver enzymes occurred in approximately 7% of patients outside the setting of CRS and resulted in treatment discontinuation in less than 1% of patients.

Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during THIS DRUG treatment. Interrupt THIS DRUG if the transaminases rise to greater than 5 times the upper limit of normal or if bilirubin rises to more than 3 times the upper limit of normal.

F. Pancreatitis

Fatal pancreatitis has been reported in patients receiving THIS DRUG in combination with dexamethasone in clinical trials and the postmarketing setting.

Evaluate patients who develop signs and symptoms of pancreatitis. Management of pancreatitis may require either temporary interruption or discontinuation of THIS DRUG and dexamethasone.

G. Leukoencephalopathy

Cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving THIS DRUG, especially in patients with prior treatment with cranial irradiation and antileukemic chemotherapy (including systemic high-dose methotrexate or intrathecal cytarabine). The clinical significance of these imaging changes is unknown.

H. Preparation and Administration Errors

Preparation and administration errors have occurred with THIS DRUG treatment. Follow instructions for preparation (including admixing) and administration strictly to minimize medication errors (including underdose and overdose).

I. Immunization

The safety of immunization with live viral vaccines during or following THIS DRUG therapy has not been studied. Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of THIS DRUG treatment, during treatment, and until immune recovery following last cycle of THIS DRUG.

J. CD19-Negative Relapse

Relapse of CD19-negative B-precursor ALL has been reported in patients receiving THIS DRUG in clinical trials and the post-marketing setting. THIS DRUG is not recommended in patients with CD19-negative disease including those who have relapsed with CD19-negative disease after prior anti-CD19 therapy. Particular attention should be given to assessment of CD19 expression at the time of bone marrow testing.

K. Lineage Switch from ALL to Acute Myeloid Leukemia (AML)

Lineage switch from ALL to AML has been rarely reported in relapsed patients receiving THIS DRUG, including those with no immunophenotypic and/or cytogenetic abnormalities at initial diagnosis. All relapsed patients should be monitored for presence of AML.

5. Drug-Drug Interactions

No formal drug interaction studies have been conducted with THIS DRUG. Initiation of THIS DRUG treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug-drug interaction risk is during the first 9 days of the first cycle

and the first 2 days of the second cycle in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity (eg, warfarin) or drug concentrations (eg, cyclosporine). Adjust the dose of the concomitant drug as needed.

6. Use in Pregnancy, Nursing Mothers, Pediatric Population, Geriatric Population, Hepatic Impairment, and Renal Impairment

A. Pregnancy

Based on its mechanism of action, THIS DRUG may cause fetal harm including B-cell lymphocytopenia when administered to a pregnant woman. There are no data on the use of THIS DRUG in pregnant women. In animal reproduction studies, a murine surrogate molecule administered to pregnant mice crossed the placental barrier. Advise pregnant women of the potential risk to a fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions
Due to the potential for B-cell lymphocytopenia in infants following exposure to THIS DRUG in-utero, the infant's B lymphocytes should be monitored before the initiation of live virus vaccination.

Pre-clinical data
Animal reproduction studies have not been conducted with blinatumomab. In embryo-fetal developmental toxicity studies, a murine surrogate molecule was administered intravenously to pregnant mice during the period of organogenesis. The surrogate molecule crossed the placental barrier and did not cause embryo-fetal toxicity or teratogenicity. The expected depletions of B and T cells were observed in the pregnant mice, but hematological effects were not assessed in fetuses.

B. Nursing Mothers

There is no information regarding the presence of THIS DRUG in human milk, the effects on the breastfed infant, or the effects on milk production. Because many drugs are excreted in

human milk and because of the potential for serious adverse reactions in breastfed infants from THIS DRUG, including B-cell lymphocytopenia, advise patients not to breastfeed during treatment with THIS DRUG and for at least 48 hours after the last dose.

C. Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating THIS DRUG treatment.

Contraception

Females

THIS DRUG may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with THIS DRUG and for at least 48 hours after the last dose.

D. Pediatric Population

The safety and efficacy of THIS DRUG have been established in pediatric patients with relapsed or refractory B-cell precursor ALL. Use of THIS DRUG is supported by a single-arm trial in pediatric patients with relapsed or refractory B-cell precursor ALL. This study included pediatric patients in the following age groups: 10 infants (1 month up to less than 2 years), 40 children (2 years up to less than 12 years), and 20 adolescents (12 years to less than 18 years). No differences in efficacy were observed between the different age subgroups.

In general, the adverse reactions in THIS DRUG-treated pediatric patients were similar in type to those seen in adult patients with relapsed or refractory B-cell precursor ALL. Adverse reactions that were observed more frequently (≥ 10%) in the pediatric population compared to the adult population were pyrexia (80% vs. 61%), hypertension (26% vs. 8%), anemia (41% vs. 24%), infusion-related reaction (49% vs. 34%), thrombocytopenia (34% vs. 21%), leukopenia (24% vs. 11%), and weight increased (17% vs. 6%).

In pediatric patients less than 2 years old (infants), the incidence of neurologic toxicities was not significantly different than for the other age groups, but its manifestations were different; the only event terms reported were agitation, headache, insomnia, somnolence, and irritability. Infants also had an increased incidence of hypokalemia (50%) compared to other pediatric age cohorts (15-20%) or adults (17%).

The steady-state concentrations of THIS DRUG were comparable in adult and pediatric patients at the equivalent dose levels based on BSA-based regimens.

E. Geriatric Population

Of the total number of patients with ALL treated in clinical studies of THIS DRUG approximately 12% were 65 and over, while 2% were 75 and older. No overall differences in safety or effectiveness were observed between elderly patients (65 and over) and younger patients, and the other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, elderly patients experienced a higher rate of serious infections and neurological toxicities, including cognitive disorder, encephalopathy and confusion.

F. Hepatic Impairment

No formal pharmacokinetic studies using THIS DRUG have been conducted in patients with hepatic impairment.

G. Renal Impairment

No formal pharmacokinetic studies using THIS DRUG have been conducted in patients with renal impairment.

Pharmacokinetic analyses showed an approximately 2-fold difference in mean THIS DRUG clearance values between patients with moderate renal impairment (CrCL ranging from 30 to 59 mL/min, N = 21) and normal renal function (CrCL more than 90 mL/min, N = 215). However, high interpatient variability was discerned (CV% up to 96.8%), and clearance values in renal impaired patients were essentially within the range observed in patients with normal renal function. There is no information available in patients with severe renal impairment (CrCL less than 30 mL/min) or patients on hemodialysis.

7. Overdosage

Overdoses have been observed, including one adult patient who received 133-fold the recommended therapeutic dose of THIS DRUG delivered over a short duration.

In the dose evaluation phase of a study in pediatric and adolescent patients with relapsed or refractory B-cell precursor ALL, 1 patient experienced a fatal cardiac failure event in the setting of life-threatening cytokine release syndrome (CRS) at a 30 $\mu g/m^2$/day (higher than the maximum tolerated/recommended) dose.

Overdoses resulted in adverse reactions which were consistent with the reactions observed at the recommended dosage and included fever, tremors, and headache. In the event of overdose, interrupt the infusion, monitor the patient for signs of adverse reaction, and provide supportive care. Consider re-initiation of THIS DRUG at the recommended dosage when all adverse reactions have resolved and no earlier than 12 hours after interruption of the infusion.

8. Cautions in Administration

A. Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and re-initiation (eg, if treatment is interrupted for 4 or more hours), supervision by a healthcare professional or hospitalization is recommended.

B. The infusion pump should be programmable, lockable, non-elastomeric, and have an alarm. THIS DRUG must be administered using IV tubing that contains a sterile, non-pyrogenic, low protein-binding, 0.2 micron in-line filter.

C. Do not flush THIS DRUG′S infusion line or intravenous catheter, especially when changing infusion bags. Flushing when changing bags or at completion of infusion can result in excess dosage and complications thereof. When administering via a multi-lumen venous catheter, THIS DRUG should be infused through a dedicated lumen.

D. Reconstitution and preparation of solution for infusion

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

1) Aseptic preparation

Strictly observe aseptic technique when preparing the solution for infusion since THIS DRUG's vials do not contain antimicrobial preservatives. To prevent accidental contamination, prepare THIS DRUG according to aseptic standards, including but not limited to:

- Prepare in an appropriate aseptic facility.
- Prepare THIS DRUG in an ISO Class 5 laminar flow hood or better.

- Ensure that the admixing area has appropriate environmental specifications, confirmed by periodic monitoring.
- Ensure that personnel are appropriately trained in aseptic manipulations and admixing of oncology drugs.
- Ensure that personnel wear appropriate protective clothing and gloves.
- Ensure that gloves and surfaces are disinfected.

2) Package Content

- 1 package THIS DRUG includes 1 vial of THIS DRUG (lyophilized powder) and 1 vial of IV Solution Stabilizer.
- **Do not use IV Solution Stabilizer for reconstitution of THIS DRUG.** IV Solution Stabilizer is provided with the THIS DRUG package and is used to coat the IV bag prior to addition of reconstituted THIS DRUG to prevent adhesion of THIS DRUG to IV bags and IV tubing.
- More than 1 package of THIS DRUG may be needed to prepare some of the recommended doses.

3) IV infusion bags and tubing sets for use

- Use polyolefin, PVC DEHP-free (di-ethylhexylphthalate-free), or ethyl vinyl acetate (EVA) infusion bags/pump cassettes.
- Use polyolefin, PVC DEHP-free, or EVA IV tubing sets.

THIS DRUG is incompatible with di-ethylhexylphthalate (DEHP) due to the possibility of particle formation, leading to a cloudy solution.

4) Preparation and Administration of THIS DRUG as 24-Hour or 48-Hour Infusion

A. Reconstitution of THIS DRUG for 24-Hours or 48-Hours Infusion

1. Determine the number of THIS DRUG vials needed for a dose and infusion duration.
2. Reconstitute each THIS DRUG vial with 3 mL of preservative-free Sterile Water for Injection by directing the water along the walls of the THIS DRUG vial and not directly on the lyophilized powder. The resulting concentration per THIS DRUG vial is 12.5 µg/mL.
    - **Do not reconstitute THIS DRUG vials with IV Solution Stabilizer.**
3. Gently swirl contents to avoid excess foaming.
    - **Do not shake.**
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, colorless to slightly yellow.

- **Do not use if solution is cloudy or has precipitated.**

B. Preparation of THIS DRUG Infusion Bag for 24- or 48-Hour Infusion

Verify the prescribed dose and infusion duration for each THIS DRUG infusion bag. To minimize errors, **use the specific volumes described in Table 7 to Table 8 to prepare the THIS DRUG infusion bag.**

- Table 7 for patients weighing 45 kg or more
- Table 8 for patients weighing less than 45 kg

1. **Aseptically add 270 mL 0.9% Sodium Chloride Injection to the IV bag.**
2. **Aseptically transfer 5.5 mL IV Solution Stabilizer to the IV bag containing 0.9% Sodium Chloride Injection.** Gently mix the contents of the bag to avoid foaming. Discard the vial containing the unused IV Solution Stabilizer.
3. **Aseptically transfer the required volume of reconstituted THIS DRUG** solution into the IV bag containing 0.9% Sodium Chloride Injection and IV Solution Stabilizer. Gently mix the contents of the bag to avoid foaming.
    - Refer to Table 7 for patients weighing 45 kg or more for the specific volume of reconstituted THIS DRUG.
    - Refer to Table 8 for patients weighing less than 45 kg (dose based on BSA) for the specific volume of reconstituted THIS DRUG.
    - Discard the vial containing unused THIS DRUG.
4. Under aseptic conditions, attach the IV tubing to the IV bag with the sterile 0.2 micron in-line filter.
    - Ensure that the IV tubing is compatible with the infusion pump.
5. Remove air from the IV bag. This is particularly important for use with an ambulatory infusion pump.
6. **Prime the IV tubing only with the solution in the bag containing the FINAL prepared THIS DRUG solution for infusion. Do not prime with 0.9% Sodium Chloride Injection.**
7. Store refrigerated at 2°C to 8°C if not used immediately.

Table 7. For Patients Weighing 45 kg or More: Volumes to Add to IV Bag

0.9% Sodium Chloride Injection (starting volume)			270 mL	
IV Solution Stabilizer (fixed volume for 24-hour and 48-hour infusion durations)			5.5 mL	
Infusion Duration	**Dose**	**Infusion Rate**	**Reconstituted THIS DRUG**	
			Volume	**Vials**
24 hours	9 µg /day	10 mL/hour	0.83 mL	1
	28 µg /day	10 mL/hour	2.6 mL	1
48 hours	9 µg /day	5 mL/hour	1.7 mL	1
	28 µg /day	5 mL/hour	5.2 mL	2

Table 8. For Patients Weighing Less Than 45 kg: Volumes to Add to IV Bag

0.9% Sodium Chloride Injection (starting volume)	270 mL
IV Solution Stabilizer (fixed volume for 24-hour and 48-hour infusion)	5.5 mL

Infusion Duration	**Dose**	**Infusion Rate**	**BSA (m^2)**	**Reconstituted THIS DRUG**	
				Volume	**Vials**
24 hours	5 µg /m^2/day	10 mL/hour	1.5 – 1.59	0.7 mL	1
			1.4 – 1.49	0.66 mL	1
			1.3 – 1.39	0.61 mL	1
			1.2 – 1.29	0.56 mL	1
			1.1 – 1.19	0.52 mL	1
			1 – 1.09	0.47 mL	1
			0.9 – 0.99	0.43 mL	1
			0.8 – 0.89	0.38 mL	1
			0.7 – 0.79	0.33 mL	1
			0.6 – 0.69	0.29 mL	1
			0.5 – 0.59	0.24 mL	1
			0.4 – 0.49	0.2 mL	1

0.9% Sodium Chloride Injection (starting volume)	270 mL
IV Solution Stabilizer (fixed volume for 24-hour and 48-hour infusion)	5.5 mL

Infusion Duration	**Dose**	**Infusion Rate**	**BSA (m^2)**	**Reconstituted THIS DRUG**	
				Volume	**Vials**
24 hours	15 µg /m^2/day	10 mL/hour	1.5 – 1.59	2.1 mL	1
			1.4 – 1.49	2 mL	1
			1.3 – 1.39	1.8 mL	1
			1.2 – 1.29	1.7 mL	1
			1.1 – 1.19	1.6 mL	1
			1 – 1.09	1.4 mL	1
			0.9 – 0.99	1.3 mL	1
			0.8 – 0.89	1.1 mL	1
			0.7 – 0.79	1 mL	1
			0.6 – 0.69	0.86 mL	1
			0.5 – 0.59	0.72 mL	1
			0.4 – 0.49	0.59 mL	1

0.9% Sodium Chloride Injection (starting volume)	270 mL
IV Solution Stabilizer (fixed volume for 24-hour and 48-hour infusion)	5.5 mL

Infusion Duration	**Dose**	**Infusion Rate**	**BSA (m^2)**	**Reconstituted THIS DRUG**	
				Volume	**Vials**
48 hours	5 µg /m^2/day	5 mL/hour	1.5 – 1.59	1.4 mL	1
			1.4 – 1.49	1.3 mL	1
			1.3 – 1.39	1.2 mL	1
			1.2 – 1.29	1.1 mL	1
			1.1 – 1.19	1 mL	1
			1 – 1.09	0.94 mL	1
			0.9 – 0.99	0.85 mL	1
			0.8 – 0.89	0.76 mL	1
			0.7 – 0.79	0.67 mL	1
			0.6 – 0.69	0.57 mL	1
			0.5 – 0.59	0.48 mL	1
			0.4 – 0.49	0.39 mL	1

0.9% Sodium Chloride Injection (starting volume)	270 mL
IV Solution Stabilizer (fixed volume for 24-hour and 48-hour infusion)	5.5 mL

Infusion Duration	**Dose**	**Infusion Rate**	**BSA (m^2)**	**Reconstituted THIS DRUG**	
				Volume	**Vials**
48 hours	15 µg /m^2/day	5 mL/hour	1.5 – 1.59	4.2 mL	2
			1.4 – 1.49	3.9 mL	2
			1.3 – 1.39	3.7 mL	2
			1.2 – 1.29	3.4 mL	2
			1.1 – 1.19	3.1 mL	2
			1 – 1.09	2.8 mL	1
			0.9 – 0.99	2.6 mL	1
			0.8 – 0.89	2.3 mL	1
			0.7 – 0.79	2 mL	1
			0.6 – 0.69	1.7 mL	1
			0.5 – 0.59	1.4 mL	1
			0.4 – 0.49	1.2 mL	1

C. Administration of THIS DRUG for 24-Hour or 48-Hour Infusion

- Administer THIS DRUG as a continuous intravenous infusion at a constant flow rate using an infusion pump. The pump should be programmable, lockable, non-elastomeric, and have an alarm.
- The starting volume (270 mL) is more than the volume administered to the patient (240 mL) to account for the priming of the IV tubing and to ensure that the patient will receive the full dose of THIS DRUG.
- Infuse prepared THIS DRUG final infusion solution according to the instructions on the pharmacy label on the prepared bag at one of the following constant infusion rates:
  - Infusion rate of 10 mL/hour for a duration of 24 hours, OR
  - Infusion rate of 5 mL/hour for a duration of 48 hours
- Administer prepared THIS DRUG final infusion solution using IV tubing that contains a sterile, non-pyrogenic, low protein-binding, 0.2 micron in-line filter.
- **Important Note: Do not flush the THIS DRUG infusion line or intravenous catheter, especially when changing infusion bags. Flushing when changing bags**

or at completion of infusion can result in excess dosage and complications thereof. When administering via a multi-lumen venous catheter, infuse THIS DRUG through a dedicated lumen.

- At the end of the infusion, discard any unused THIS DRUG solution in the IV bag and IV tubing in accordance with local requirements.

9. Cautions for Storage and Handling

A. Storage of Reconstituted THIS DRUG

The information in Table 9 indicates the storage time for the reconstituted THIS DRUG vial and prepared infusion bag.

Table 9. Storage time for reconstituted THIS DRUG and Prepared THIS DRUG infusion bag

	Maximum Storage Time	
	Room Temperature 23°C to 27°C	Refrigerated 2°C to 8°C
Reconstituted THIS DRUG Vial	4 hours	24 hours
Prepared THIS DRUG Infusion Bag	48 hours*	10 days

* Storage time includes infusion time. If the prepared THIS DRUG infusion bag is not administered within the time frames and temperatures indicated, it must be discarded; it should not be refrigerated again.

B. Storage and Handling

- Store THIS DRUG and IV Solution Stabilizer vials in the original package refrigerated at 2~8°C and protect from light until time of use. Do not freeze.
- THIS DRUG and IV solution Stabilizer vials may be stored for maximum of 8 hours at room temperature [23°C ~27°C] in the original carton to protect from light.
- Ship in packaging that has been validated to maintain temperature of the contents at 2~8°C. Do not freeze.
- At the end of the infusion, any unused drug in the IV bag and IV lines should be disposed of in accordance with the institutes' standard procedures.

[STORAGE CONDITION]

Store at 2°~8°C

Store in hermetic container to protect from light.

[PACKAGING UNIT]

1 Vial/box ([Vial (38.5 μg) x 1 + IV solution stabilizer (10 mL) x 1]/box)

[EXPIRY DATE]

Refer to the outer package (Year/Month/Date)

[MARKETING APPLICATION HOLDER]

Amgen Inc. Thousand Oaks, CA 91320-1799, USA

[MANUFACTURER]

1) Drug substance **Lonza Biologics plc.**
228 Bath Road, Slough, Berkshire, SL1 4DX, UK

2) Drug product **Boehringer Ingelheim Pharma GmbH & Co., KG**
Birkendorfer Strasse 65, D-88397 Biberach an der Riss, Germany
Amgen Technology Ireland
Pottery Road, Dun Laoghaire, Co. Dublin, Ireland

3) Packaging **Amgen Manufacturing Ltd. (AML)**
State Road 31, Kilometer 24.6, Juncos, Puerto Rico 00777, USA

[IMPORTER]

Amgen Korea Limited 20th floor, Eulji-ro 5-gil 19, Jung-gu, Seoul, Korea

- If products are decomposed, deteriorated, damaged, contaminated or expired, they can be exchanged at the pharmacy, clinic, hospital, or wholesaler where purchased. Please contact the facility where you bought the product for return or exchange.
- You will be compensated for consumers' damages as per the Consumer Injury Compensation Rule
- Application for Remedy for Side Effects of Drugs: The Korea Institute of Drug Safety and Risk Management (Tel: 1644-6223, www.drugsafe.or.kr)
- You can find the latest product information after the following revision date on the MFDS on-line library website (http://nedrug.mfds.go.kr) or the importer website (www.amgen.co.kr)
- Importer contact phone: 00798 611 3554 (toll free) / 02-3434-4899 / Medinfo.JAPAC@amgen.com

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