

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

***APPLICATION NUMBER:***

**125557Orig1s007**

***Trade Name:*** Blincyto® 35 mcg/vial

***Generic or Proper Name:*** blinatumomab for injection

***Sponsor:*** Amgen, Inc.

***Approval Date:*** May 3, 2017

This Prior Approval supplemental biologics application provides for updates to US Prescribing Information and Medication Guide to incorporate new admixing instructions to prepare single, 7-day Blincyto infusion bags in conjunction with Bacteriostatic 0.9% Sodium Chloride, USP (containing 0.9% benzyl alcohol) as the preservative.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 125557Orig1s007

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**125557Orig1s007**

**APPROVAL LETTER**



BLA 125557/S-007

**SUPPLEMENT APPROVAL**

Amgen, Inc.  
Attention: Jennifer Woo, PhD  
Senior Manager, Regulatory Affairs  
One Amgen Center Drive  
Mail Stop 17-1-C  
Thousand Oaks, CA 91320-1799

Dear Dr. Woo:

Please refer to your Supplemental Biologics License Application (sBLA), dated December 1, 2016, received December 1, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for Blincyto<sup>®</sup> (blinatumomab) for injection, 35 mcg/vial.

This Prior Approval supplemental biologics application provides for updates to US Prescribing Information and Medication Guide to incorporate new admixing instructions to prepare single, 7-day BLINCYTO infusion bags in conjunction with Bacteriostatic 0.9% Sodium Chloride, USP (containing 0.9% benzyl alcohol) as the preservative.

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the prescribing information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, MD  
Division Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANN T FARRELL  
05/03/2017

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*APPLICATION NUMBER:*

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**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BLINCYTO® safely and effectively. See full prescribing information for BLINCYTO.

**BLINCYTO® (blinatumomab) for injection, for intravenous use**  
**Initial U.S. Approval: 2014**

### **WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES**

*See full prescribing information for complete boxed warning.*

- Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.3, 5.1)
- Neurological toxicities, which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. (2.3, 5.2)

### RECENT MAJOR CHANGES

- Indications and Usage (1) 8/2016
- Dosage and Administration (2.1, 2.3) 8/2016
- Dosage and Administration (2.2, 2.4, 2.5, 2.6, 2.7) 5/2017
- Warnings and Precautions (5.1, 5.2, 5.7, 5.8, 5.11) 8/2016
- Warnings and Precautions (5.12) 5/2017

### INDICATIONS AND USAGE

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit in subsequent trials. (1)

### DOSAGE AND ADMINISTRATION

- Dosage
  - A single cycle of treatment consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days). (2.1)
  - For patients greater than or equal to 45 kg, in Cycle 1, administer BLINCYTO at 9 mcg/day on Days 1-7 and at 28 mcg/day on Days 8- 28. For subsequent cycles, administer BLINCYTO at 28 mcg/day on Days 1-28. (2.1)
  - For patients less than 45 kg, in Cycle 1, administer BLINCYTO at 5 mcg/m<sup>2</sup>/day on Days 1-7 and at 15 mcg/m<sup>2</sup>/day on Days 8-28. For subsequent cycles, administer BLINCYTO at 15 mcg/m<sup>2</sup>/day on Days 1-28. (2.1)
- Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle. (2.2)
- Premedicate with dexamethasone. (2.2)

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES

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- 5.9 Leukoencephalopathy
- 5.10 Preparation and Administration Errors
- 5.11 Immunization

- Refer to Full Prescribing Information for important preparation and administration information. (2.4, 2.5, 2.6)
- Administer as a continuous intravenous infusion at a constant flow rate using an infusion pump. (2.5, 2.6)
  - See Section 2.5 for infusion over 24 hours or 48 hours.
  - See Section 2.6 for infusion over 7 days using Bacteriostatic 0.9% Sodium Chloride, USP (containing 0.9% benzyl alcohol). This option is not recommended for patients weighing less than 22 kg.

### DOSAGE FORMS AND STRENGTHS

For injection: 35 mcg of lyophilized powder in a single-dose vial for reconstitution. (3)

### CONTRAINDICATIONS

Known hypersensitivity to blinatumomab or to any component of the product formulation. (4)

### WARNINGS AND PRECAUTIONS

- Infections: Monitor patients for signs or symptoms; treat appropriately. (5.3)
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO is being administered. (5.6)
- Pancreatitis: Evaluate patients who develop signs and symptoms of pancreatitis. Management of pancreatitis may require either temporary interruption or discontinuation of BLINCYTO. (5.8)
- Preparation and Administration Errors: Strictly follow instructions for preparation (including admixing) and administration. (5.10)
- Risk of Serious Adverse Reactions in Pediatric Patients due to Benzyl Alcohol Preservative: Use BLINCYTO prepared with preservative-free saline for patients weighing less than 22 kg. (5.12, 8.4)

### ADVERSE REACTIONS

The most common adverse reactions (≥ 20%) were pyrexia, headache, nausea, edema, hypokalemia, anemia, febrile neutropenia, neutropenia, thrombocytopenia, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2017

- 5.12 Risk of Serious Adverse Reactions in Pediatric Patients due to Benzyl Alcohol Preservative

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## FULL PRESCRIBING INFORMATION

### WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGICAL TOXICITIES

- Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended [see *Dosage and Administration (2.3), Warnings and Precautions (5.1)*].
- Neurological toxicities, which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended [see *Dosage and Administration (2.3), Warnings and Precautions (5.2)*].

## 1 INDICATIONS AND USAGE

BLINCYTO is indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit in subsequent trials [see *Clinical Studies (14)*].

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosage

- A single cycle of treatment of BLINCYTO consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days).
- A treatment course consists of up to 2 cycles of BLINCYTO for induction followed by 3 additional cycles for consolidation treatment (up to a total of 5 cycles).
- See Table 1 for the recommended daily dose by patient weight. Patients greater than or equal to 45 kg receive a fixed-dose and for patients less than 45 kg, the dose is calculated using the patient's body surface area (BSA).

**Table 1. BLINCYTO Recommended Dosage**

Patient Weight	Cycle 1*			Subsequent Cycles*	
	Days 1-7	Days 8-28	Days 29-42	Days 1-28	Days 29-42
Greater than or equal to 45 kg (fixed-dose)	9 mcg/day	28 mcg/day	14-day treatment-free interval	28 mcg/day	14-day treatment-free interval
Less than 45 kg (BSA-based dose)	5 mcg/m <sup>2</sup> /day (not to exceed 9 mcg/day)	15 mcg/m <sup>2</sup> /day (not to exceed 28 mcg/day)		15 mcg/m <sup>2</sup> /day (not to exceed 28 mcg/day)	

\*A single cycle of treatment of BLINCYTO consists of 28 days of continuous intravenous infusion followed by a 14-day treatment-free interval (total 42 days).

## 2.2 Special Considerations

- 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.
- Premedicate with dexamethasone.
  - For adult patients, premedicate with 20 mg dexamethasone 1 hour prior to the first dose of BLINCYTO of each cycle, prior to a step dose (such as Cycle 1 Day 8), and when restarting an infusion after an interruption of 4 or more hours.
  - For pediatric patients, premedicate with 5 mg/m<sup>2</sup> of dexamethasone, to a maximum dose of 20 mg prior to the first dose of BLINCYTO in the first cycle, prior to a step dose (such as Cycle 1 Day 8), and when restarting an infusion after an interruption of 4 or more hours in the first cycle.
- For administration of BLINCYTO:
  - See Section 2.5 for infusion over 24 hours or 48 hours.
  - See Section 2.6 for infusion over 7 days using Bacteriostatic 0.9% Sodium Chloride, USP (containing 0.9% benzyl alcohol). This option is available for patients weighing greater than or equal to 22 kg. It is not recommended for use in patients weighing less than 22 kg.

## 2.3 Dosage Adjustments

If the interruption after an adverse event 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 event is longer than 7 days, start a new cycle.

<b>Toxicity</b>	<b>Grade*</b>	<b>Patients Greater Than or Equal to 45 kg</b>	<b>Patients Less Than 45 kg</b>
Cytokine Release Syndrome (CRS)	Grade 3	Withhold BLINCYTO until resolved, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.	Withhold BLINCYTO until resolved, then restart BLINCYTO at 5 mcg/m <sup>2</sup> /day. Escalate to 15 mcg/m <sup>2</sup> /day after 7 days if the toxicity does not recur.
	Grade 4	Discontinue BLINCYTO permanently.	
Neurological Toxicity	Seizure	Discontinue BLINCYTO permanently if more than one seizure occurs.	
	Grade 3	Withhold BLINCYTO until no more than Grade 1 (mild) and for at least 3 days, then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently.	Withhold BLINCYTO until no more than Grade 1 (mild) and for at least 3 days, then restart BLINCYTO at 5 mcg/m <sup>2</sup> /day. Escalate to 15 mcg/m <sup>2</sup> /day after 7 days if the toxicity does not recur. If the toxicity occurred at 5 mcg/m <sup>2</sup> /day, or if the toxicity takes more than 7 days to resolve, discontinue BLINCYTO permanently.
	Grade 4	Discontinue BLINCYTO permanently.	
Other Clinically Relevant Adverse Reactions	Grade 3	Withhold BLINCYTO until no more than Grade 1 (mild), then restart BLINCYTO at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue BLINCYTO permanently.	Withhold BLINCYTO until no more than Grade 1 (mild), then restart BLINCYTO at 5 mcg/m <sup>2</sup> /day. Escalate to 15 mcg/m <sup>2</sup> /day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue BLINCYTO permanently.
	Grade 4	Consider discontinuing BLINCYTO permanently.	

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

## 2.4 Preparation

**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) [see Warnings and Precautions (5.10)].**

BLINCYTO can be infused over 24 hours (preservative-free) or 48 hours (preservative-free), or 7 days (with preservative). The choice between these options for the infusion duration should be made by the treating physician considering the frequency of the infusion bag changes and the weight of the patient. The 7- day infusion is not recommended for patients weighing less than 22 kg.

For preparation, reconstitution, and administration of BLINCYTO:

- See Section 2.5 for infusion over 24 hours or 48 hours.
- See Section 2.6 for infusion over 7 days using Bacteriostatic 0.9% Sodium Chloride, USP (containing 0.9% benzyl alcohol). This option is available for patients weighing greater than or equal to 22 kg. It is not recommended for patients weighing less than 22 kg.

Call 1-800-77-AMGEN (1-800-772-6436) if you have questions about the reconstitution and preparation of BLINCYTO.

### 2.4.1 Aseptic Preparation

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

- Prepare BLINCYTO in a USP <797> compliant facility.
- Prepare BLINCYTO 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.

### 2.4.2 Package Content

1 package BLINCYTO includes 1 vial of BLINCYTO and 1 vial of IV Solution Stabilizer.

- **Do not use IV Solution Stabilizer for reconstitution of BLINCYTO.** IV Solution Stabilizer is provided with the BLINCYTO package and is used to coat the IV bag prior to addition of reconstituted BLINCYTO to prevent adhesion of BLINCYTO to IV bags and IV tubing.
- More than 1 package of BLINCYTO may be needed to prepare some of the prescribed doses.

### 2.4.3 Incompatibility Information

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

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

## 2.5 24-Hour or 48-Hour Infusion of BLINCYTO

### 2.5.1 Preparation of BLINCYTO Infusion Bag for 24- or 48-Hour Infusion

Verify the prescribed dose and infusion duration for each BLINCYTO infusion bag. To minimize errors, use the specific volumes described in Tables 2 to 4 to prepare the BLINCYTO infusion bag.

- Table 2 for patients weighing greater than or equal to 45 kg
  - Tables 3 and 4 for patients weighing less than 45 kg
1. Aseptically add 270 mL 0.9% Sodium Chloride Injection, USP to the IV bag.
  2. Aseptically transfer 5.5 mL IV Solution Stabilizer to the IV bag containing 0.9% Sodium Chloride Injection, USP. Gently mix the contents of the bag to avoid foaming. Discard the vial containing the unused IV Solution Stabilizer.
  3. Aseptically transfer reconstituted BLINCYTO [see Dosage and Administration (2.5.2)] into the IV bag containing 0.9% Sodium Chloride Injection, USP and IV Solution Stabilizer. Gently mix the contents of the bag to avoid foaming.
    - Refer to Tables 2 to 4 for the specific volume of reconstituted BLINCYTO.
  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. **Prime the IV tubing only with the prepared solution for infusion. Do not prime with 0.9% Sodium Chloride Injection, USP.**
  6. Store at 2°C to 8°C if not used immediately [see Dosage and Administration (2.7)].

**Table 2. For Patients Weighing Greater Than or Equal to 45 kg: Volumes to Add to IV Bag**

0.9% Sodium Chloride Injection, USP (starting volume)		270 mL	
IV Solution Stabilizer		5.5 mL	
Dose	Infusion Duration	Infusion Rate	Reconstituted BLINCYTO
9 mcg/day	24 hours	10 mL/hour	0.83 mL
	48 hours	5 mL/hour	1.7 mL
28 mcg/day	24 hours	10 mL/hour	2.6 mL
	48 hours	5 mL/hour	5.2 mL*

\* 2 packages of BLINCYTO are needed for preparation of 28 mcg/day dose infused over 48 hours at a rate of 5 mL/hour.

**Table 3. For Patients Weighing Less Than 45 kg: Volumes to Add to IV Bag for 5 mcg/m<sup>2</sup>/day Dose**

<b>0.9% Sodium Chloride Injection, USP (starting volume)</b>				270 mL
<b>IV Solution Stabilizer</b>				5.5 mL
<b>Dose</b>	<b>Infusion Duration</b>	<b>Infusion Rate</b>	<b>BSA (m<sup>2</sup>)</b>	<b>Reconstituted BLINCYTO</b>
<b>5 mcg/m<sup>2</sup>/day</b>	24 hours	10 mL/hour	1.5 – 1.59	0.7 mL
			1.4 – 1.49	0.66 mL
			1.3 – 1.39	0.61 mL
			1.2 – 1.29	0.56 mL
			1.1 – 1.19	0.52 mL
			1 – 1.09	0.47 mL
			0.9 – 0.99	0.43 mL
			0.8 – 0.89	0.38 mL
			0.7 – 0.79	0.33 mL
			0.6 – 0.69	0.29 mL
			0.5 – 0.59	0.24 mL
			0.4 – 0.49	0.2 mL
<b>5 mcg/m<sup>2</sup>/day</b>	48 hours	5 mL/hour	1.5 – 1.59	1.4 mL
			1.4 – 1.49	1.3 mL
			1.3 – 1.39	1.2 mL
			1.2 – 1.29	1.1 mL
			1.1 – 1.19	1 mL
			1 – 1.09	0.94 mL
			0.9 – 0.99	0.85 mL
			0.8 – 0.89	0.76 mL
			0.7 – 0.79	0.67 mL
			0.6 – 0.69	0.57 mL
			0.5 – 0.59	0.48 mL
			0.4 – 0.49	0.39 mL

**Table 4. For Patients Weighing Less Than 45 kg: Volumes to Add to IV Bag for 15 mcg/m<sup>2</sup>/day Dose**

<b>0.9% Sodium Chloride Injection, USP (starting volume)</b>				270 mL
<b>IV Solution Stabilizer</b>				5.5 mL
<b>Dose</b>	<b>Infusion Duration</b>	<b>Infusion Rate</b>	<b>BSA (m<sup>2</sup>)</b>	<b>Reconstituted BLINCYTO</b>
<b>15 mcg/m<sup>2</sup>/day</b>	24 hours	10 mL/hour	1.5 – 1.59	2.1 mL
			1.4 – 1.49	2 mL
			1.3 – 1.39	1.8 mL
			1.2 – 1.29	1.7 mL
			1.1 – 1.19	1.6 mL
			1 – 1.09	1.4 mL
			0.9 – 0.99	1.3 mL
			0.8 – 0.89	1.1 mL
			0.7 – 0.79	1 mL
			0.6 – 0.69	0.86 mL
			0.5 – 0.59	0.72 mL
			0.4 – 0.49	0.59 mL
<b>15 mcg/m<sup>2</sup>/day</b>	48 hours	5 mL/hour	1.5 – 1.59	4.2 mL*
			1.4 – 1.49	3.9 mL*
			1.3 – 1.39	3.7 mL*
			1.2 – 1.29	3.4 mL*
			1.1 – 1.19	3.1 mL*
			1 – 1.09	2.8 mL
			0.9 – 0.99	2.6 mL
			0.8 – 0.89	2.3 mL
			0.7 – 0.79	2 mL
			0.6 – 0.69	1.7 mL
			0.5 – 0.59	1.4 mL
			0.4 – 0.49	1.2 mL

\* 2 packages of BLINCYTO are needed for preparation of 15 mcg/m<sup>2</sup>/day dose infused over 48 hours at a rate of 5 mL/hour for patients with a BSA greater than 1.09 m<sup>2</sup>.

### 2.5.2 Reconstitution of BLINCYTO

1. Add 3 mL of preservative-free Sterile Water for Injection, USP by directing the water along the walls of the BLINCYTO vial and not directly on the lyophilized powder (resulting in a final BLINCYTO concentration of 12.5 mcg/mL).
  - **Do not reconstitute BLINCYTO with IV Solution Stabilizer.**
2. Gently swirl contents to avoid excess foaming. **Do not shake.**
3. 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.**

### 2.5.3 Administration

- Administer BLINCYTO 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.
- Prepared BLINCYTO infusion bags [see *Dosage and Administration (2.5.1)*] should be infused over 24 hours or 48 hours.
- 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 BLINCYTO.
- Infuse BLINCYTO 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
- The BLINCYTO solution must be administered using IV tubing that contains a sterile, non-pyrogenic, low protein-binding, 0.2 micron in-line filter.
- **Important Note: Do not flush the BLINCYTO 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, BLINCYTO should be infused through a dedicated lumen.**
- At the end of the infusion, any unused BLINCYTO solution in the IV bag and IV tubing should be disposed of in accordance with local requirements.

### 2.6 7-Day Infusion of BLINCYTO using Bacteriostatic Saline

This option is not recommended for use in patients weighing less than 22 kg [see *Warnings and Precautions (5.12)* and *Use in Specific Populations (8.4)*].

#### 2.6.1 Preparation of BLINCYTO Infusion Bag for 7-Day Infusion

Verify the prescribed dose and infusion duration for each BLINCYTO infusion bag. To minimize errors, **use the specific volumes described in Table 5 to prepare the BLINCYTO infusion bag.**

1. **Aseptically add 90 mL Bacteriostatic 0.9% Sodium Chloride, USP to the empty IV bag.**
2. **Aseptically transfer 2.2 mL IV Solution Stabilizer to the IV bag containing the saline solution.** Gently mix the contents of the bag to avoid foaming. Discard the vial containing the unused IV Solution Stabilizer.
3. **Aseptically transfer reconstituted BLINCYTO** [see *Dosage and Administration (2.6.2)*] into the IV bag containing the saline solution and IV Solution Stabilizer. Gently mix the contents of the bag to avoid foaming.
  - Refer to Table 5 for the specific volume of reconstituted BLINCYTO.
4. **Aseptically add 0.9% Sodium Chloride Injection, USP to the IV bag to a final volume of 110 mL resulting in 0.74% benzyl alcohol.** Gently mix the contents of the bag to avoid foaming.
  - Refer to Table 5 for the specific volume of 0.9% Sodium Chloride Injection, USP
5. Under aseptic conditions, attach the IV tubing to the IV bag. An in-line filter is not required for a 7-day bag.
  - Ensure that the IV tubing is compatible with the infusion pump.
6. Remove air from the IV bag. This is particularly important for use with an ambulatory infusion pump. **Prime the IV tubing only with the prepared solution for infusion. Do not prime with 0.9% Sodium Chloride Injection, USP.**
7. Store at 2°C to 8°C if not used immediately [see *Dosage and Administration (2.7)*].

**Table 5. For 7-Day Infusion: Volumes to Add to IV Bag for 28 mcg/day and 15 mcg/m<sup>2</sup>/day;  
Not Recommended for Patients Less Than 22 kg**

Bacteriostatic 0.9% Sodium Chloride (starting volume)		90 mL			
IV Solution Stabilizer		2.2 mL			
Reconstituted BLINCYTO		Specific volume listed below in table			
Quantity Sufficient (qs) with 0.9% Sodium Chloride, USP to a Final Volume of 110 mL					
Infusion Duration		7 days			
Infusion Rate		0.6 mL/hour			
Patient Weight	Dose	BSA (m <sup>2</sup> )	Number of BLINCYTO Packages	Reconstituted BLINCYTO	0.9% Sodium Chloride Injection, USP to qs to a Final Volume of 110 mL
Greater than or equal to 45 kg (fixed-dose)	28 mcg/day		6	16.8 mL	1 mL
22-45 kg (BSA-based dose)	15 mcg/m <sup>2</sup> /day	1.5 – 1.59	5	14 mL	3.8 mL
		1.4 – 1.49	5	13.1 mL	4.7 mL
		1.30 – 1.39	5	12.2 mL	5.6 mL
		1.20 – 1.29	5	11.3 mL	6.5 mL
		1.10 – 1.19	4	10.4 mL	7.4 mL
		1 – 1.09	4	9.5 mL	8.3 mL
		0.9 – 0.99	4	8.6 mL	9.2 mL

### 2.6.2 Reconstitution of BLINCYTO

1. Add 3 mL of preservative-free Sterile Water for Injection, USP by directing the water along the walls of the BLINCYTO vial and not directly on the lyophilized powder (resulting in a final BLINCYTO concentration of 12.5 mcg/mL).
  - **Do not reconstitute BLINCYTO with IV Solution Stabilizer.**
2. Gently swirl contents to avoid excess foaming. **Do not shake.**
3. 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.**

### 2.6.3 Administration

- Administer BLINCYTO 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.
- Prepared BLINCYTO infusion bags [see *Dosage and Administration (2.6.1)*] should be infused over 7 days.
- The final volume of infusion solution (110 mL) will be more than the volume administered to the patient (100 mL) to account for the priming of the IV tubing and to ensure that the patient will receive the full dose of BLINCYTO.
- Infuse BLINCYTO solution according to the instructions on the pharmacy label on the prepared bag at an infusion rate of 0.6 mL/hour for a duration of 7 days.
- **Important Note: Do not flush the BLINCYTO 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, BLINCYTO should be infused through a dedicated lumen.**
- At the end of the infusion, any unused BLINCYTO solution in the IV bag and IV tubing should be disposed of in accordance with local requirements.

### 2.7 Storage Requirements

The information in Table 6 indicates the storage time for the reconstituted BLINCYTO vial and prepared infusion bag.

Store lyophilized BLINCYTO and IV Solution Stabilizer vials for a maximum of 8 hours at room temperature in the original carton to protect from light [see *How Supplied/Storage and Handling (16.2)*].

**Table 6. Storage Time for Reconstituted BLINCYTO Vial and Prepared BLINCYTO Infusion Bag**

	Maximum Storage Time	
	Room Temperature 23°C to 27°C (73°F to 81°F)	Refrigerated 2°C to 8°C (36°F to 46°F)
<b>Reconstituted BLINCYTO Vial</b>	4 hours	24 hours
<b>Prepared BLINCYTO Infusion Bag (Preservative-Free)</b>	48 hours*	8 days
<b>Prepared BLINCYTO Infusion Bag (with Preservative)</b>	7 days*	14 days

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

## 3 DOSAGE FORMS AND STRENGTHS

For injection: 35 mcg of lyophilized powder in a single-dose vial for reconstitution.

## 4 CONTRAINDICATIONS

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

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Cytokine Release Syndrome

Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO.

Infusion reactions have occurred with the BLINCYTO infusion and may be clinically indistinguishable from manifestations of CRS.

Serious adverse events that may be associated with CRS included pyrexia, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, and increased total bilirubin; these events infrequently led to BLINCYTO discontinuation. Life-threatening or fatal CRS was reported in patients receiving BLINCYTO. 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.

Patients should be closely monitored for signs or symptoms of these events. Management of these events may require either temporary interruption or discontinuation of BLINCYTO [*see Dosage and Administration (2.3)*].

### 5.2 Neurological Toxicities

In patients receiving BLINCYTO in clinical trials, neurological toxicities have occurred in approximately 64% of patients. The median time to onset of any neurological toxicity was 4 days. The most common ( $\geq 10\%$ ) manifestations of neurological toxicity were headache, tremor, dizziness, and altered state of consciousness; the neurological toxicity profile varied by age group [*see Use in Specific Populations (8.4, 8.5)*]. Grade 3 or higher (severe, life-threatening, or fatal) neurological toxicities following initiation of BLINCYTO administration occurred in approximately 17% of patients and included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. The majority of events resolved following interruption of BLINCYTO, but some resulted in treatment discontinuation.

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

Monitor patients receiving BLINCYTO for signs and symptoms of neurological toxicities, and interrupt or discontinue BLINCYTO as recommended [*see Dosage and Administration (2.3)*].

### 5.3 Infections

In patients receiving BLINCYTO in clinical trials, 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 BLINCYTO. Monitor patients for signs and symptoms of infection and treat appropriately.

#### **5.4 Tumor Lysis Syndrome**

Tumor lysis syndrome (TLS), which may be life-threatening or fatal, has been observed in patients receiving BLINCYTO. Appropriate prophylactic measures, including pretreatment nontoxic cyto-reduction and on-treatment hydration, should be used for the prevention of TLS during BLINCYTO treatment. Monitor for signs or symptoms of TLS. Management of these events may require either temporary interruption or discontinuation of BLINCYTO [see *Dosage and Administration (2.3)*].

#### **5.5 Neutropenia and Febrile Neutropenia**

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

#### **5.6 Effects on Ability to Drive and Use Machines**

Due to the potential for neurologic events, including seizures, patients receiving BLINCYTO are at risk for loss of consciousness [see *Warnings and Precautions (5.2)*]. Advise patients to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO is being administered.

#### **5.7 Elevated Liver Enzymes**

Treatment with BLINCYTO was associated with transient elevations in liver enzymes. In clinical trials, the median time to onset of elevated liver enzymes was 3 days.

In patients receiving BLINCYTO, although the majority of these events were observed in the setting of CRS, some were observed outside of this setting. For these events, the median time to onset was 15 days. Grade 3 or greater elevations in liver enzymes occurred in approximately 6% of patients outside the setting of CRS and resulted in treatment discontinuation in less than 1% of patients.

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

#### **5.8 Pancreatitis**

Fatal pancreatitis has been reported in patients receiving BLINCYTO 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 BLINCYTO and dexamethasone [see *Dosage and Administration (2.3)*].

## 5.9 Leukoencephalopathy

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

## 5.10 Preparation and Administration Errors

Preparation and administration errors have occurred with BLINCYTO treatment. Follow instructions for preparation (including admixing) and administration strictly to minimize medication errors (including underdose and overdose) [see *Dosage and Administration (2.4)*].

## 5.11 Immunization

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

## 5.12 Risk of Serious Adverse Reactions in Pediatric Patients due to Benzyl Alcohol Preservative

Serious and fatal adverse reactions including “gasping syndrome” can occur in neonates and infants treated with benzyl alcohol-preserved drugs, including BLINCYTO (with preservative). The “gasping syndrome” is characterized by central nervous system depression, metabolic acidosis, and gasping respirations.

When prescribing BLINCYTO (with preservative) for pediatric patients, consider the combined daily metabolic load of benzyl alcohol from all sources including BLINCYTO (with preservative) (contains 7.4 mg of benzyl alcohol per mL) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known [see *Use in Specific Populations (8.4)*].

Due to the addition of bacteriostatic saline, 7-day bags of BLINCYTO solution for infusion with preservative contain benzyl alcohol and are not recommended for use in any patients weighing less than 22 kg [see *Dosage and Administration (2.6)* and *Use in Specific Populations (8.4)*].

## 6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Cytokine Release Syndrome [see *Warnings and Precautions (5.1)*]
- Neurological Toxicities [see *Warnings and Precautions (5.2)*]
- Infections [see *Warnings and Precautions (5.3)*]
- Tumor Lysis Syndrome [see *Warnings and Precautions (5.4)*]
- Neutropenia and Febrile Neutropenia [see *Warnings and Precautions (5.5)*]
- Effects on Ability to Drive and Use Machines [see *Warnings and Precautions (5.6)*]
- Elevated Liver Enzymes [see *Warnings and Precautions (5.7)*]
- Pancreatitis [see *Warnings and Precautions (5.8)*]
- Leukoencephalopathy [see *Warnings and Precautions (5.9)*]

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to BLINCYTO in clinical trials in which 282 patients (212 adult and 70 pediatric patients) with relapsed or refractory ALL were treated with a recommended dose and schedule. All patients received at least one dose of BLINCYTO. The most common adverse reactions ( $\geq 20\%$ ) in the safety population were pyrexia, headache, nausea, edema, hypokalemia, anemia, febrile neutropenia, neutropenia, thrombocytopenia, and abdominal pain. For some adverse reactions, there were differences in incidence rates by age subgroup [*see Use in Specific Populations (8.4, 8.5)*].

The safety population included 225 patients weighing 45 kg or more and 57 patients weighing less than 45 kg. In general, the adverse reactions in the BLINCYTO-treated patients less than 45 kg were similar in type to those seen in patients greater than or equal to 45 kg.

### *Patients Greater Than or Equal to 45 kg*

The median age of patients greater than or equal to 45 kg was 34 years (range: 11 to 79 years), 63% were male, 79% were White, 3% were Asian, and 3% were Black or African American.

Serious adverse reactions were reported in 61% of patients. The most common serious adverse reactions ( $\geq 2\%$ ) included febrile neutropenia, pyrexia, sepsis, pneumonia, device-related infection, neutropenia, tremor, overdose, encephalopathy, infection, confusion, and headache. Adverse reactions of Grade 3 or higher were reported in 80% of patients. Discontinuation of therapy due to adverse reactions occurred in 16% of patients treated with BLINCYTO. The adverse reactions reported most frequently as the reason for discontinuation of treatment included encephalopathy and sepsis. Fatal adverse events occurred in 12% of patients. The majority of the fatal events were infections. No fatal adverse events occurred on treatment among patients in remission.

### *Patients Less Than 45 kg*

The median age of patients less than 45 kg was 6 years (range: 7 months to 64 years), 68% were male, and 77% were White.

Serious adverse reactions were reported in 51% of patients. The most common serious adverse reactions ( $\geq 2\%$ ) included pyrexia, febrile neutropenia, cytokine release syndrome, convulsion, device-related infection, hypoxia, sepsis, and overdose. Adverse reactions of Grade 3 or higher were reported in 88% of patients. Discontinuation of therapy due to adverse reactions occurred in 5% of patients treated with BLINCYTO. Adverse reactions that led to discontinuation of treatment were CRS and fungal infection. Three patients experienced a fatal adverse event within 30 days of the last dose of BLINCYTO (2 infection and 1 multi-organ failure after undergoing subsequent HSCT).

The adverse reactions with  $\geq 10\%$  incidence for any grade or  $\geq 5\%$  incidence for Grade 3 or higher are summarized in Table 7.

**Table 7. Adverse Reactions With  $\geq 10\%$  Incidence for Any Grade or  $\geq 5\%$  Incidence for Grade 3 or Higher**

Adverse Reaction	Patients Greater Than or Equal to 45 kg (N = 225)		Patients Less Than 45 kg (N = 57)	
	Any Grade <sup>1</sup> (%)	Grade 3 or Higher <sup>1</sup> (%)	Any Grade <sup>1</sup> (%)	Grade 3 or Higher <sup>1</sup> (%)
<i>Blood and lymphatic system disorders</i>				
Febrile neutropenia	25	23	19	18
Anemia <sup>2</sup>	21	16	42	35
Neutropenia <sup>3</sup>	19	18	32	32
Thrombocytopenia <sup>4</sup>	16	12	35	35
Leukopenia <sup>5</sup>	14	12	26	21
<i>Cardiac disorders</i>				
Arrhythmia <sup>6</sup>	19	2	11	0
<i>Gastrointestinal disorders</i>				
Nausea	26	0	30	0
Constipation	20	0	9	2
Diarrhea <sup>7</sup>	19	1	19	4
Abdominal pain <sup>8</sup>	19	2	23	4
Vomiting	13	0	26	2
<i>General disorders and administration site conditions</i>				
Pyrexia	64	7	75	16
Edema <sup>9</sup>	30	2	11	0
Fatigue	16	1	9	0
Chills	15	0	2	0
Chest pain	10	1	4	0
<i>Immune system disorders</i>				
Infusion-related reactions <sup>10</sup>	34	4	44	12
Cytokine release syndrome <sup>11</sup>	13	3	11	4
<i>Infections and infestations</i>				
Infections – pathogen unspecified <sup>12</sup>	45	27	42	21
Bacterial infections <sup>12</sup>	19	12	11	5
Fungal infections <sup>12</sup>	14	7	7	5
Viral infections <sup>12</sup>	13	4	9	2
<i>Investigations</i>				
Decreased				

immunoglobulins <sup>13</sup>	12	2	5	0
Increased weight	11	0	18	5
<i>Metabolism and nutrition disorders</i>				
Hypokalemia <sup>14</sup>	27	8	21	16
Hypomagnesemia <sup>15</sup>	12	0	9	0
Hyperglycemia <sup>16</sup>	12	7	11	4
Decreased appetite	10	3	4	0
Hypophosphatemia	6	4	16	5
Hypocalcemia	5	2	11	4
<i>Musculoskeletal and connective tissue disorders</i>				
Back pain	15	2	16	4
Pain in extremity	12	1	11	4
Bone pain	11	3	9	0
Arthralgia	10	2	4	0
<i>Nervous system disorders</i>				
Headache	36	4	28	2
Tremor <sup>17</sup>	19	1	7	0
Dizziness	13	< 1	5	0
Altered state of consciousness <sup>18</sup>	10	1	7	4
<i>Psychiatric disorders</i>				
Insomnia	14	0	5	0
<i>Respiratory, thoracic, and mediastinal disorders</i>				
Cough	20	< 1	18	0
Dyspnea <sup>19</sup>	15	5	4	4
Epistaxis	10	< 1	9	2
<i>Skin and subcutaneous tissue disorders</i>				
Rash <sup>20</sup>	21	2	11	0
<i>Vascular disorders</i>				
Hypotension <sup>21</sup>	13	3	12	2
Hypertension	9	5	25	5

1	Grading is based on the Common Terminology Criteria for Adverse Events (CTCAE). Grade 3 is severe, Grade 4 is life-threatening, and Grade 5 is fatal.
2	Anemia includes anemia and hemoglobin decreased.
3	Neutropenia includes neutropenia and neutrophil count decreased.
4	Thrombocytopenia includes thrombocytopenia and platelet count decreased.
5	Leukopenia includes leukopenia and white blood cell count decreased.
6	Arrhythmia includes tachycardia, sinus tachycardia, bradycardia, sinus bradycardia, supraventricular tachycardia, atrial fibrillation, ventricular fibrillation, atrial tachycardia, and ventricular extrasystoles.
7	Diarrhea includes diarrhea, colitis, enteritis, gastroenteritis, and neutropenic colitis.
8	Abdominal pain includes abdominal pain, abdominal pain upper, gastrointestinal pain, and abdominal pain lower.
9	Edema includes peripheral edema, edema, and generalized edema.
10	Infusion-related reactions is a composite term that includes infusion related reaction and the following events occurring within the first 48 hours of infusion: pyrexia, hypotension, cytokine release syndrome, hypertension, myalgia, maculo-papular rash, rash, face swelling, and tachypnea.
11	Cytokine release syndrome includes cytokine release syndrome, capillary leak syndrome, cytokine storm, and infusion-related reaction.
12	Higher level group term.
13	Decreased immunoglobulins includes immunoglobulins decreased, blood immunoglobulin G decreased, blood immunoglobulin A decreased, blood immunoglobulin M decreased, and hypogammaglobulinemia.
14	Hypokalemia includes hypokalemia and blood potassium decreased.
15	Hypomagnesemia includes hypomagnesemia and blood magnesium decreased.
16	Hyperglycemia includes hyperglycemia and blood glucose increased.
17	Tremor includes tremor and resting tremor.
18	Altered state of consciousness includes somnolence, mental status changes, lethargy, depressed level of consciousness, altered state of consciousness, stupor, and disturbance in attention.
19	Dyspnea includes dyspnea, respiratory failure, wheezing, dyspnea exertional, bronchospasm, acute respiratory failure, bronchial hyperreactivity, and respiratory distress.
20	Rash includes rash, erythema, maculo-papular rash, generalized rash, macular rash, papular rash, dermatitis diaper, erythematous rash, and vesicular rash.
21	Hypotension includes hypotension, circulatory collapse, and hypovolemic shock.

For patients weighing greater than or equal to 45 kg and patients less than 45 kg, additional important adverse reactions that did not meet the threshold criteria for inclusion in Table 7 were, in each weight cohort respectively: leukocytosis (2%, 4%), lymphopenia (1%, 2%), increased gamma-glutamyl-transferase (6%, 2%), tumor lysis syndrome (4%, 0%), hypoalbuminemia (4%, 7%), encephalopathy (5%, 2%), paresthesia (5%, 2%), aphasia (4%, 0%), convulsion (2%, 4%), memory impairment (2%, 0%), cognitive disorder (1%, 0%), speech disorder (< 1%, 0%), confusional state (7%, 0%), and disorientation (3%, 0%), respectively.

Hypersensitivity reactions related to BLINCYTO treatment were hypersensitivity (1%) and bronchospasm (< 1%).

Selected laboratory abnormalities worsening from baseline Grade 0-2 to treatment-related maximal Grade 3-4 are shown in Table 8.

**Table 8. Selected Laboratory Abnormalities Worsening from Baseline Grade 0-2 to Treatment-Related Maximal Grade 3-4<sup>1</sup>**

	<b>Patients Greater Than or Equal to 45 kg Grade 3 or 4 (%)</b>	<b>Patients Less Than 45 kg Grade 3 or 4 (%)</b>
<b>Hematology</b>		
Decreased lymphocyte count	90	88
Decreased white blood cell count	63	79
Decreased hemoglobin	38	64

Decreased neutrophil count	67	97
Decreased platelet count	57	74
<b>Chemistry</b>		
Increased ALT	21	36
Increased bilirubin	13	5
Increased AST	11	18
Decreased potassium	9	30
Decreased calcium	8	4
Decreased albumin	2	2

<sup>1</sup> Includes only patients who had both baseline and at least one laboratory measurement during the study available.

## 6.2 Postmarketing Experience

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

- Fatal pancreatitis has been reported in patients receiving BLINCYTO in combination with dexamethasone [see *Warnings and Precautions (5.8)*].

## 6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of BLINCYTO has been evaluated using either an electrochemiluminescence detection technology (ECL) or an enzyme-linked immunosorbent assay (ELISA) screening immunoassay for the detection of binding anti-blinatumomab antibodies. For patients whose sera tested positive in the screening immunoassay, an *in vitro* biological assay was performed to detect neutralizing antibodies.

In clinical studies, less than 1% of patients treated with BLINCYTO tested positive for binding anti-blinatumomab antibodies. All patients who tested positive for binding antibodies also tested positive for neutralizing anti-blinatumomab antibodies. Anti-blinatumomab antibody formation may affect pharmacokinetics of BLINCYTO.

If formation of anti-blinatumomab antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

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

## 7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with BLINCYTO. Initiation of BLINCYTO treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug-drug interaction risk is during the first 9 days of the first cycle and the first 2 days of the second

cycle in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity (eg, warfarin) or drug concentrations (eg, cyclosporine). Adjust the dose of the concomitant drug as needed [see *Clinical Pharmacology (12.2, 12.3)*].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Based on its mechanism of action, BLINCYTO may cause fetal harm including B-cell lymphocytopenia when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no data on the use of BLINCYTO in pregnant women. In animal reproduction studies, a murine surrogate molecule administered to pregnant mice crossed the placental barrier [see *Data*]. Advise pregnant women of the potential risk to a fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. 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 BLINCYTO in-utero, the infant's B lymphocytes should be monitored before the initiation of live virus vaccination [see *Warnings and Precautions (5.11)*].

#### Data

##### *Animal Data*

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

### **8.2 Lactation**

#### Risk Summary

There is no information regarding the presence of blinatumomab in human milk, the effects on the breastfed infant, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from BLINCYTO, including B-cell lymphocytopenia, advise patients not to breastfeed during and for at least 48 hours after treatment with BLINCYTO.

### 8.3 Females and Males of Reproductive Potential

Based on its mechanism of action, BLINCYTO may cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

#### Pregnancy Testing

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

#### Contraception

##### *Females*

Advise females of reproductive potential to use effective contraception during treatment and for at least 48 hours after the last dose of BLINCYTO.

### 8.4 Pediatric Use

The safety and efficacy of BLINCYTO have been established in pediatric patients. Use of BLINCYTO 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 BLINCYTO-treated pediatric patients were similar in type to those seen in adult patients [see *Adverse Reactions (6.1)*]. Adverse reactions that were observed more frequently ( $\geq 10\%$ ) in the pediatric population compared to the adult population were anemia (41% vs 18%), thrombocytopenia (21% vs. 11%), vomiting (24% vs. 13%), pyrexia (80% vs. 62%), and hypertension (26% vs. 8%). 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 (23%).

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

#### Benzyl Alcohol Toxicity in Pediatric Patients

Serious adverse reactions including fatal reactions and the “gasping syndrome” occurred in premature neonates and infants in the neonatal intensive care unit who received drugs containing benzyl alcohol as a preservative. In these cases, benzyl alcohol dosages of 99 to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 to 1.378 mmol/L). Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low-birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol.

When prescribing BLINCYTO (with preservative) in pediatric patients consider the combined daily metabolic load of benzyl alcohol from all sources including BLINCYTO (with preservative) (contains 7.4 mg of benzyl alcohol per mL) and other drugs containing benzyl alcohol. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known [see *Warnings and Precautions (5.12)*].

Due to the addition of bacteriostatic saline, 7-day bags of BLINCYTO solution for infusion contain benzyl alcohol and are not recommended for use in patients weighing less than 22 kg. Prepare BLINCYTO solution for infusion with preservative-free saline (24- or 48-hour bags) for use in patients weighing less than 22 kg [see *Dosage and Administration* (2.5)].

## 8.5 Geriatric Use

Of the total number of patients with relapsed or refractory ALL in clinical studies of BLINCYTO, treated at the recommended dose and schedule, approximately 10% were 65 and over, while 1% were 75 and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, elderly patients experienced a higher rate of neurological toxicities, including cognitive disorder, encephalopathy, confusion, and serious infections [see *Warnings and Precautions* (5.2, 5.3)].

## 10 OVERDOSAGE

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

In the dose evaluation phase of the Phase 1/2 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 mcg/m<sup>2</sup>/day (higher than the maximum tolerated/recommended) dose [see *Warnings and Precautions* (5.1) and *Adverse Reactions* (6)].

Overdoses resulted in adverse reactions which were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, interrupt the infusion, monitor the patient for signs of toxicity, and provide supportive care [see *Warnings and Precautions* (5.10)]. Consider re-initiation of BLINCYTO at the correct therapeutic dose when all toxicities have resolved and no earlier than 12 hours after interruption of the infusion [see *Dosage and Administration* (2.1)].

## 11 DESCRIPTION

BLINCYTO (blinatumomab) is a bispecific CD19-directed CD3 T-cell engager that binds to CD19 (expressed on cells of B-lineage origin) and CD3 (expressed on T cells). BLINCYTO is produced in Chinese hamster ovary cells. It consists of 504 amino acids and has a molecular weight of approximately 54 kilodaltons.

Each BLINCYTO package contains 1 vial BLINCYTO and 1 vial IV Solution Stabilizer.

BLINCYTO is supplied in a single-dose vial as a sterile, preservative-free, white to off-white lyophilized powder for intravenous administration. Each single-dose vial of BLINCYTO contains 35 mcg blinatumomab, citric acid monohydrate (3.35 mg), lysine hydrochloride (23.23 mg), polysorbate 80 (0.64 mg), trehalose dihydrate (95.5 mg), and sodium hydroxide to adjust pH to 7.0. After reconstitution with 3 mL of preservative-free Sterile Water for Injection, USP, the resulting concentration is 12.5 mcg/mL blinatumomab.

IV Solution Stabilizer is supplied in a single-dose vial as a sterile, preservative-free, colorless to slightly yellow, clear solution. Each single-dose vial of IV Solution Stabilizer contains citric acid monohydrate

(52.5 mg), lysine hydrochloride (2283.8 mg), polysorbate 80 (10 mg), sodium hydroxide to adjust pH to 7.0, and water for injection.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Blinatumomab is a bispecific CD19-directed CD3 T-cell engager that binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. It activates endogenous T cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B cells. Blinatumomab mediates the formation of a synapse between the T-cell and the tumor cell, upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, which result in redirected lysis of CD19+ cells.

### 12.2 Pharmacodynamics

During the continuous intravenous infusion over 4 weeks, the pharmacodynamic response was characterized by T-cell activation and initial redistribution, reduction in peripheral B cells, and transient cytokine elevation.

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

Peripheral B cell counts decreased to less than or equal to 10 cells/microliter during the first treatment cycle at doses  $\geq 5$  mcg/m<sup>2</sup>/day or  $\geq 9$  mcg/day in the majority of patients. No recovery of peripheral B-cell counts was observed during the 2-week BLINCYTO-free period between treatment cycles. Incomplete depletion of B cells occurred at doses of 0.5 mcg/m<sup>2</sup>/day and 1.5 mcg/m<sup>2</sup>/day and in a few patients at higher doses.

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

### 12.3 Pharmacokinetics

The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 90 mcg/m<sup>2</sup>/day (approximately equivalent to 9 to 162 mcg/day) in adult patients. Following continuous intravenous infusion, the steady-state serum concentration ( $C_{ss}$ ) was achieved within a day and remained stable over time. The increase in mean  $C_{ss}$  values was approximately proportional to the dose in the range tested. At the clinical doses of 9 mcg/day and 28 mcg/day for the treatment of relapsed/refractory ALL, the mean (SD)  $C_{ss}$  was 211 (258) pg/mL and 621 (502) pg/mL, respectively.

#### *Distribution*

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

### *Metabolism*

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

### *Elimination*

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

### *Gender, Age, and Body Surface Area*

Results of population pharmacokinetic analyses indicate that age (0.62 to 80 years of age) and gender do not influence the pharmacokinetics of blinatumomab. Body surface area (0.37 to 2.70 m<sup>2</sup>) influences the pharmacokinetics of blinatumomab, however the clinical relevance of this effect is unknown.

### *Hepatic Impairment*

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

### *Renal Impairment*

No formal pharmacokinetic studies of blinatumomab have been conducted in patients with renal impairment.

Pharmacokinetic analyses showed an approximately 2-fold difference in mean blinatumomab clearance values between patients with moderate renal 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 95.6%), 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.

### *Drug Interactions*

Transient elevation of cytokines may suppress CYP450 enzyme activities [*see Drug Interactions (7) and Clinical Pharmacology (12.2)*].

### *Specific Populations*

**Pediatrics:** The pharmacokinetics of blinatumomab appear linear over a dose range from 5 to 30 mcg/m<sup>2</sup>/day in pediatric patients. At the recommended doses, the mean (SD) steady state concentration (C<sub>ss</sub>) values were 162 (179) and 533 (392) pg/mL at 5 and 15 mcg/m<sup>2</sup>/day doses, respectively. The estimated mean (SD) volume of distribution (V<sub>z</sub>), clearance (CL) and terminal half-life (t<sub>1/2,z</sub>) were 3.91 (3.36) L/m<sup>2</sup>, 1.88 (1.90) L/hour/m<sup>2</sup> and 2.19 (1.53) hours, respectively.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

No carcinogenicity or genotoxicity studies have been conducted with blinatumomab.

No studies have been conducted to evaluate the effects of blinatumomab on fertility. A murine surrogate molecule had no adverse effects on male and female reproductive organs in a 13-week repeat-dose toxicity study in mice.

## 14. CLINICAL STUDIES

### 14.1 Relapsed/Refractory Acute Lymphoblastic Leukemia

#### Study 1

Study 1 was an open-label, multicenter, single-arm study. Eligible patients were  $\geq 18$  years of age with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL (relapsed with first remission duration of  $\leq 12$  months in first salvage or relapsed or refractory after first salvage therapy or relapsed within 12 months of allogeneic hematopoietic stem cell transplantation [HSCT], and had  $\geq 10\%$  blasts in bone marrow).

BLINCYTO was administered as a continuous intravenous infusion. The recommended dose for this study was determined to be 9 mcg/day on Days 1-7 and 28 mcg/day on Days 8-28 for Cycle 1, and 28 mcg/day on Days 1-28 for subsequent cycles. Dose adjustment was possible in case of adverse events. The treated population included 185 patients who received at least 1 infusion of BLINCYTO; the median number of treatment cycles was 2 (range: 1 to 5). Patients who responded to BLINCYTO but later relapsed had the option to be retreated with BLINCYTO. Among treated patients, the median age was 39 years (range: 18 to 79 years), 63 out of 185 (34.1%) had undergone HSCT prior to receiving BLINCYTO, and 32 out of 185 (17.3%) had received more than 2 prior salvage therapies.

Efficacy was based on the complete remission (CR) rate, duration of CR, and proportion of patients with an MRD-negative CR/CR with partial hematological recovery (CR/CRh\*) within 2 cycles of treatment with BLINCYTO. Seventy-seven out of 185 (41.6%) evaluable patients achieved CR/CRh\* within the first 2 treatment cycles, with the majority of responses (81%, 62 out of 77) occurring within Cycle 1 of treatment. See Table 9 for efficacy results from this study. The HSCT rate among those who achieved CR/CRh\* was 39% (30 out of 77).

**Table 9. Study 1: Efficacy Results in Patients  $\geq 18$  Years of Age With Philadelphia Chromosome-Negative Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia (ALL)**

	N = 185		
	CR <sup>1</sup>	CRh* <sup>2</sup>	CR/CRh*
n (%)	60 (32.4)	17 (9.2)	77 (41.6)
[95% CI]	[25.7 – 39.7]	[5.4 – 14.3]	[34.4 – 49.1]
<b>MRD response<sup>3</sup></b>			
n1/n2 (%) <sup>4</sup>	48/60 (80.0)	10/17 (58.8)	58/77 (75.3)
[95% CI]	[67.7 – 89.2]	[32.9 – 81.6]	[64.2 – 84.4]
<b>DOR/RFS<sup>5</sup></b>			
Median (months) (range)	6.7 (0.46 – 16.5)	5.0 (0.13 – 8.8)	5.9 (0.13 – 16.5)

<sup>1</sup> CR (complete remission) was defined as  $\leq 5\%$  of blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets  $> 100,000/\text{microliter}$  and absolute neutrophil counts [ANC]  $> 1,000/\text{microliter}$ ).

<sup>2</sup> CRh\* (complete remission with partial hematological recovery) was defined as  $\leq 5\%$  of blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets  $> 50,000/\text{microliter}$  and ANC  $> 500/\text{microliter}$ ).

<sup>3</sup> MRD (minimal residual disease) response was defined as MRD by PCR  $< 1 \times 10^{-4}$ .

<sup>4</sup> n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. Six CR/CRh\* responders with missing MRD data were considered as MRD-nonresponders.

<sup>5</sup> DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh\* to relapse or death, whichever is earlier. Relapse was defined as hematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.

## Study 2

Study 2 was an open-label, multicenter, single-arm study in pediatric patients with relapsed or refractory B-cell precursor ALL (second or later bone marrow relapse, any marrow relapse after allogeneic HSCT, or refractory to other treatments, and had > 25% blasts in bone marrow). BLINCYTO was administered at 5 mcg/m<sup>2</sup>/day on Days 1-7 and 15 mcg/m<sup>2</sup>/day on Days 8-28 for Cycle 1, and 15 mcg/m<sup>2</sup>/day on Days 1-28 for subsequent cycles. Dose adjustment was possible in case of adverse events. Patients who responded to BLINCYTO but later relapsed had the option to be retreated with BLINCYTO.

Among the 70 treated patients, the median age was 8 years (range: 7 months to 17 years), 40 out of 70 (57.1%) had undergone allogeneic HSCT prior to receiving BLINCYTO, and 39 out of 70 (55.7%) had refractory disease. The median number of treatment cycles was 1 (range: 1 to 5).

Twenty-three out of 70 (32.9%) patients achieved CR/CRh\* within the first 2 treatment cycles with 17 out of 23 (73.9%) occurring within Cycle 1 of treatment. See Table 10 for the efficacy results from the study. The HSCT rate among those who achieved CR/CRh\* was 48% (11 out of 23).

**Table 10. Study 2: Efficacy Results in Patients < 18 Years of Age With Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia (ALL)**

	N = 70		
	CR <sup>1</sup>	CRh* <sup>2</sup>	CR/CRh*
n (%)	12 (17.1)	11 (15.7)	23 (32.9)
[95% CI]	[9.2 – 28.0]	[8.1 – 26.4]	[22.1 – 45.1]
<b>MRD response<sup>3</sup></b>			
n1/n2 (%) <sup>4</sup>	6/12 (50.0)	4/11 (36.4)	10/23 (43.5)
[95% CI]	[21.1 – 78.9]	[10.9 – 69.2]	[23.2 – 65.5]
<b>DOR/RFS<sup>5</sup></b>			
Median (months) (range)	6.0 (0.5 – 12.1)	3.5 (0.5 – 16.4)	6.0 (0.5 – 16.4)

<sup>1</sup> CR (complete remission) was defined as ≤ 5% of blasts in the bone marrow, no evidence of circulating blasts or extra-medullary disease, and full recovery of peripheral blood counts (platelets > 100,000/microliter and absolute neutrophil counts [ANC] > 1,000/microliter).

<sup>2</sup> CRh\* (complete remission with partial hematological recovery) was defined as ≤ 5% of blasts in the bone marrow, no evidence of circulating blasts or extra-medullary disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).

<sup>3</sup> MRD (minimal residual disease) response was defined as MRD by PCR or flow cytometry < 1 x 10<sup>-4</sup>.

<sup>4</sup> n1: number of patients who achieved MRD response and the respective remission status; n2: number of patients who achieved the respective remission status. One CR/CRh\* responder with missing MRD data was considered as a MRD-nonresponder.

<sup>5</sup> DOR (duration of response)/RFS (relapse-free survival) was defined as time since first response of CR or CRh\* to relapse or death, whichever is earlier. Relapse was defined as hematological relapse (blasts in bone marrow greater than 5% following CR) or an extramedullary relapse.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

Each BLINCYTO package (NDC 55513-160-01) contains:

- One BLINCYTO 35 mcg single-dose vial containing a sterile, preservative-free, white to off-white lyophilized powder and
- One IV Solution Stabilizer 10 mL single-dose glass vial containing a sterile, preservative-free, colorless to slightly yellow, clear solution. **Do not use the IV Solution Stabilizer to reconstitute BLINCYTO.**

## 16.2 Storage and Handling

Store BLINCYTO and IV Solution Stabilizer vials in the original package refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light until time of use. Do not freeze.

Store and transport the prepared IV bag containing BLINCYTO solution for infusion at 2°C to 8°C (36°F to 46°F) conditions. Ship in packaging that has been validated to maintain temperature of the contents at 2°C to 8°C (36°F to 46°F). Do not freeze.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

### Cytokine Release Syndrome (CRS)

Advise patients of the risk of CRS and infusion reactions, and to contact their healthcare professional for signs and symptoms associated with CRS or infusion reactions (pyrexia, fatigue, nausea, vomiting, chills, hypotension, rash, and wheezing) [*see Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].

### Neurological Toxicities

Advise patients of the risk of neurological toxicities, and to contact their healthcare professional for signs and symptoms associated with this event (convulsions, speech disorders, and confusion) [*see Warnings and Precautions (5.2) and Adverse Reactions (6.1)*].

### Infections

Advise patients of the risk of infections, and to contact their healthcare professional for signs or symptoms of infection [*see Warnings and Precautions (5.3) and Adverse Reactions (6.1)*].

Inform patients of the importance of keeping the skin clean around the intravenous catheter to reduce the risk of infection.

### Pancreatitis

Advise patients of the risk of pancreatitis and to contact their healthcare provider for signs or symptoms of pancreatitis which include severe and persistent stomach pain, with or without nausea and vomiting [*see Warnings and Precautions (5.8) and Adverse Reactions (6.2)*].

### Driving and Engaging in Hazardous Occupations

Advise patients to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO is being administered. Patients should be advised that they may experience neurological events [*see Warnings and Precautions (5.6)*].

### Reduce Risk of Infusion Pump Errors

Inform patients they should not adjust the setting on the infusion pump. Any changes to pump function may result in dosing errors. If there is a problem with the infusion pump or the pump alarms, patients should contact their doctor or nurse immediately.



BLINCYTO® (blinatumomab)

**Manufactured by:**

Amgen Inc.  
One Amgen Center Drive  
Thousand Oaks, California 91320-1799  
U.S. License No. 1080

Patent: <http://pat.amgen.com/blincyto/>

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## Medication Guide

BLINCYTO<sup>®</sup> (blin sye' toe)  
(blinatumomab)  
for injection

### What is the most important information I should know about BLINCYTO?

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

BLINCYTO 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 healthcare provider will check for these problems during treatment with BLINCYTO. Your healthcare provider may temporarily stop or completely stop your treatment with BLINCYTO, if you have severe side effects.

See “**What are the possible side effects of BLINCYTO?**” below for other side effects of BLINCYTO.

### What is BLINCYTO?

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

### Who should not receive BLINCYTO?

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

### Before receiving BLINCYTO, tell your healthcare provider about all of your medical conditions, including if you or your child:

- 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 BLINCYTO or other medications
- have a history of radiation treatment to the brain, or chemotherapy treatment
- are scheduled to receive a vaccine. You should not receive a “live vaccine” within 2 weeks before you start treatment with BLINCYTO, during treatment, and until your immune system recovers after you receive your last cycle of BLINCYTO. If you are not sure about the type of vaccine, ask your healthcare provider.
- are pregnant or plan to become pregnant. BLINCYTO may harm your unborn baby. Tell your healthcare provider if you become pregnant during treatment with BLINCYTO.
  - If you are able to become pregnant, your healthcare provider should do a pregnancy test before you start treatment with BLINCYTO.
  - Females who are able to become pregnant should use an effective form of birth control during treatment with BLINCYTO, and for at least 48 hours after the last dose of BLINCYTO.
- are breastfeeding or plan to breastfeed. It is not known if BLINCYTO passes into your breast milk. You should not breastfeed during treatment with BLINCYTO and for at least 48 hours after your last treatment.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

### How will I receive BLINCYTO?

- BLINCYTO will be given to you by intravenous (IV) infusion into your vein by an infusion pump.
- You will receive BLINCYTO by continuous IV infusion for 4 weeks (28 days), followed by a 2 week (14 days) break during which you will not receive BLINCYTO. This is one treatment cycle (42 days). After the 2 week break, your healthcare provider will decide if you will be given additional treatment cycles of BLINCYTO.
- Your healthcare provider may give you BLINCYTO in a hospital or clinic for the first 9 days of the first treatment cycle and for the first 2 days of the second cycle to check you for side effects. If you receive additional treatment cycles of BLINCYTO or if your treatment is stopped for a period of time and restarted, you may also be treated in a hospital or clinic.
- Your healthcare provider may change your dose of BLINCYTO, delay, or completely stop treatment with BLINCYTO if

you have certain side effects.

- Your healthcare provider will do blood tests during treatment with BLINCYTO to check you for side effects.
- Before you receive BLINCYTO, 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 healthcare provider 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 healthcare provider or nurse right away if you have any problems with your pump or your pump alarm sounds.**

#### What should I avoid while receiving BLINCYTO?

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

#### What are the possible side effects of BLINCYTO?

**BLINCYTO may cause serious side effects, including:**

See “What is the most important information I should know about BLINCYTO?”

- **Infections.** BLINCYTO may cause life-threatening infections that may lead to death. Tell your healthcare provider right away if you develop any signs or symptoms of an infection.
- **Low white blood cell counts (neutropenia).** Neutropenia is common with BLINCYTO treatment and may sometimes be life-threatening. Low white blood cell counts can increase your risk of infection. Your healthcare provider will do blood tests to check your white blood cell count during treatment with BLINCYTO. Tell your healthcare provider right away if you get a fever.
- **Abnormal liver blood tests.** Your healthcare provider will do blood tests to check your liver before you start BLINCYTO and during treatment with BLINCYTO.
- **Inflammation of the pancreas (pancreatitis).** Pancreatitis may happen in patients treated with BLINCYTO and corticosteroids. It may be severe and lead to death. Tell your healthcare provider right away if you have severe stomach-area pain that does not go away. The pain may happen with or without nausea and vomiting.

The most common side effects of BLINCYTO include:

- fever
- headache
- nausea
- swelling of your hands, ankles, or feet
- low blood potassium (hypokalemia)
- low red blood cell count (anemia)
- low platelet count (thrombocytopenia)
- stomach pain

These are not all the possible side effects of BLINCYTO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### How should I store BLINCYTO?

Intravenous (IV) bags containing BLINCYTO for infusion will arrive in a special package.

- Do not open the package.
- Do not freeze the package.
- The package containing BLINCYTO will be opened by your healthcare provider and stored in the refrigerator at 36°F to 46°F (2°C to 8°C) for up to 8 days.
- Do not throw away (dispose of) any BLINCYTO in your household trash. Talk with your healthcare provider about disposal of BLINCYTO and used supplies.
- **Keep BLINCYTO and all medicines out of reach of children.**

#### General information about safe and effective use of BLINCYTO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BLINCYTO for a condition for which it was not prescribed. Do not give BLINCYTO to other people even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about BLINCYTO that is written for health professionals.

#### What are the ingredients in BLINCYTO?

**Active ingredient:** blinatumomab

**Inactive ingredients:** citric acid monohydrate, lysine hydrochloride, polysorbate 80, trehalose dihydrate, sodium hydroxide and preservative-free sterile water for injection.

Manufactured by: Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799  
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For more information, go to [www.blinicyto.com](http://www.blinicyto.com) or call Amgen at 1-800-772-6436.



This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Month 2017

## IMPORTANT DRUG WARNING

**Subject: BLINCYTO® (blinatumomab) - Benzyl alcohol toxicity warning for 7-day infusion solution due to the addition of bacteriostatic saline, for pediatric patients, particularly neonates and premature infants.**

Dear Health Care Provider:

The purpose of this letter is to inform you of important safety information related to the use of BLINCYTO 7-day infusion bags containing benzyl alcohol for pediatric patients, particularly neonates and premature infants.

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit of subsequent trials.

### **Benzyl Alcohol Toxicity Warning**

BLINCYTO has recently been approved allowing the option of preparing a 7-day bag for continuous infusion, containing Bacteriostatic 0.9% Sodium Chloride, USP (containing 0.9% benzyl alcohol) as the preservative. This option is available for patients weighing  $\geq 22$  kg; however, it is not recommended for use in patients weighing  $< 22$  kg. The benzyl alcohol acceptable daily intake (ADI) set by the World Health Organization will be exceeded if 7-day infusion is used in patients who weigh  $< 22$  kg.

Benzyl alcohol has been associated with serious adverse events and death in pediatric patients. Benzyl alcohol has been given an ADI of 0-5 mg/kg/day by the World Health Organization. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants may be more likely to develop toxicity.

### **Prescriber Action**

Prepare preservative-free BLINCYTO solution for infusion (24 or 48 hour bags) for use in neonates, infants, and patients weighing  $< 22$  kg; the 7-day infusion bag containing bacteriostatic saline is not recommended for use in these patients.

### **Action Being Taken by Amgen**

Amgen has worked with the U.S. Food and Drug Administration (FDA) to include language regarding benzyl alcohol toxicity in Section 5 *Warnings and Precautions* and Section 8 *Use in Specific Populations* of the BLINCYTO prescribing information. The medication guide has also been updated to include this new information.

Additional information about this toxicity is provided in the remainder of this letter.

### **Further Information on the Safety Concern**

The preservative benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. Due to the addition of bacteriostatic saline, 7-day infusion bags of BLINCYTO solution for infusion contain benzyl alcohol. The minimum amount of benzyl alcohol at which toxicity may occur is not known. The “gaspings syndrome” (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages > 99 mg/kg/day in neonates and low-birth-weight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

### **Reporting Adverse Events**

Health care providers and patients are encouraged to report adverse events in patients taking BLINCYTO to Amgen at 1-800-77-AMGEN (1-800-772-6436). You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088.

You may also contact our medical information department at 1-800-77-AMGEN (1-800-772-6436) if you have any questions about the information contained in this letter or the safe and effective use of BLINCYTO.

This letter is not intended as a complete description of the benefits and risks related to the use of BLINCYTO. Please refer to the enclosed full prescribing information and medication guide.

Sincerely,

Paul Eisenberg, MD  
Senior Vice President of Global Medical and Chief Medical Officer

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To: \_\_\_\_\_

From: [AMGEN IMPORTANT DRUG WARNING@mminfo.messages2.com](mailto:AMGEN_IMPORTANT_DRUG_WARNING@mminfo.messages2.com)

Subject: **IMPORTANT DRUG WARNING - BLINCYTO® (blinatumomab) - Benzyl alcohol toxicity warning for 7-day infusion solution due to the addition of bacteriostatic saline, for pediatric patients, particularly neonates and premature infants.**

Dear Health Care Provider:

The purpose of this letter is to inform you of important safety information related to the use of BLINCYTO 7-day infusion bags containing benzyl alcohol for pediatric patients, particularly neonates and premature infants.

BLINCYTO is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification of clinical benefit of subsequent trials.

### **Benzyl Alcohol Toxicity Warning**

BLINCYTO has recently been approved allowing the option of preparing a 7-day bag for continuous infusion, containing Bacteriostatic 0.9% Sodium Chloride, USP (containing 0.9% benzyl alcohol) as the preservative. This option is available for patients weighing  $\geq 22$  kg; however, it is not recommended for use in patients weighing  $< 22$  kg. The benzyl alcohol acceptable daily intake (ADI) set by the World Health Organization will be exceeded if 7-day infusion is used in patients who weigh  $< 22$  kg.

Benzyl alcohol has been associated with serious adverse events and death in pediatric patients. Benzyl alcohol has been given an ADI of 0-5 mg/kg/day by the World Health Organization. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants may be more likely to develop toxicity.

### **Prescriber Action**

Prepare preservative-free BLINCYTO solution for infusion (24 or 48 hour bags) for use in neonates, infants, and patients weighing  $< 22$  kg; the 7-day infusion bag containing bacteriostatic saline is not recommended for use in these patients.

### **Action Being Taken by Amgen**

Amgen has worked with the U.S. Food and Drug Administration (FDA) to include language regarding benzyl alcohol toxicity in Section 5 *Warnings and Precautions* and Section 8 *Use in Specific Populations* of the BLINCYTO prescribing information. The medication guide has also been updated to include this new information.

Additional information about this toxicity is provided in the remainder of this letter.

### **Further Information on the Safety Concern**

The preservative benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. Due to the addition of bacteriostatic saline, 7-day infusion bags of BLINCYTO solution for infusion contain benzyl alcohol. The minimum amount of benzyl alcohol at which toxicity may occur is not known. The “gaspings syndrome” (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages > 99 mg/kg/day in neonates and low-birth-weight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

### **Reporting Adverse Events**

Health care providers and patients are encouraged to report adverse events in patients taking BLINCYTO to Amgen at 1-800-77-AMGEN (1-800-772-6436). You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088.

You may also contact our medical information department at 1-800-77-AMGEN (1-800-772-6436) if you have any questions about the information contained in this letter or the safe and effective use of BLINCYTO.

This letter is not intended as a complete description of the benefits and risks related to the use of BLINCYTO. Please refer to the full prescribing information and medication guide located at [http://pi.amgen.com/united\\_states/blincyto/blincyto\\_pi\\_hcp\\_english.pdf](http://pi.amgen.com/united_states/blincyto/blincyto_pi_hcp_english.pdf).

Sincerely,

Paul Eisenberg, MD  
Senior Vice President of Global Medical and Chief Medical Officer

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125557Orig1s007**

**MEDICAL REVIEW(S)**

**Clinical Review of Labeling  
Supplement  
Division of Hematology Products**

<b>BLA #:</b>	125557.217 Supplement 007	<b>Date Received:</b>	12/21/2016
<b>Applicant:</b>	Amgen	<b>Application Type:</b>	Commercial
<b>Related INDs:</b>	100135		
<b>Drug(s):</b>	Blincyto (Blinatumomab, AMG103, MT103, MEDI-538)		
<b>Dosage Formulation:</b>	Powder for solution for infusion		
<b>Drug Type:</b>	Approved		
<b>Drug Class:</b>	MAb (Bispecific anti-CD3 x anti-CD19)		
<b>Mechanism of Action:</b>	Bispecific single-chain antibody construct designed to link CD19 expressing B cells and T cells resulting in T cell activation and a cytotoxic T cell response against the CD19 expressing cells		
<b>Date Review Completed:</b>	4/24/2017		
<b>Primary Reviewer:</b>	Aviva Krauss, MD		
<b>Team Leader:</b>	Donna Przepiorka, MD, PhD		

**Background:** On 12/21/2016, the Applicant submitted a labeling supplement (PAS) to support the addition of new preparation instructions for single, 7-day infusion bags of blinatumomab together with bacteriostatic 0.9% saline (containing 0.9% benzyl alcohol) as the preservative. In September 2015, the Agency sent preliminary responses to the applicant's question in preparation for a Type C meeting (subsequently cancelled by the applicant). One of the clinical questions raised there was the applicant's assessment that "*a human bioequivalence study is not required as the addition of benzyl alcohol as a preservative to the blinatumomab infusion solution is not expected to affect blinatumomab systemic exposure.*" The Agency agreed that this was a reasonable approach and that the "*rationale and literature information in the meeting briefing package also seem suitable,*" but raised 2 specific concerns:

- 1) Given the association of benzyl alcohol in products used in the very young with gasping syndrome, this potential risk needed to be addressed.
- 2) The BLA should in particular provide data/information to confirm that benzyl alcohol does not affect the physiological disposition of blinatumomab.

The applicant addressed these concerns, as described below, and as a result of the first, submitted draft labeling with:

- An additional W&P regarding the risk of benzyl alcohol toxicity in younger patients,, and recommendations that its use be restricted to patients weighting  $\geq 22$  kg.
- Additional statements throughout the draft label addressing this as well ( (b) (4) (b) (4) 2.6 "7 days infusion of blincyto using bacteriostatic saline," including in table 5, (b) (4) and 8.4 "pediatric use").

**Review:** The potential risk of benzyl alcohol toxicity is real for this product in that it is approved for patients under 45 kg and has been used in children down to 9 months of age; since congenital acute lymphoblastic leukemia is a rare (41 cases/million in the US, Brown 2013) but existent entity, blinatumomab may be used in infants with disease that is refractory to or relapses after conventional therapies. This is particularly relevant since infant ALL has an outcome that is worse than that seen for ALL in children beyond the infant age group, with 5-

(Kotecha et al, 2014).

As the applicant points out, this is not the first product using a formulation that contains benzyl alcohol that is approved for pediatric use. Solu-Medrol (0.9% benzyl alcohol) is approved for multiple indications, including those seen in very young children such as Diamond Blackfan anemia (DBA) and pure red blood cell aplasia, as well as for the palliative management of leukemias and control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in various allergic states, and others. Ferrlecit (0.9% benzyl alcohol) is approved for pediatric patients 6 years of age and older with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy. Other products that contain other benzyl derivatives which have been assigned an “acceptable daily intake,” or ADI, by the WHO, as a group (“benzoic acid equivalents,” see below), include Ammonul and Diazepam. Ammonul (10% benzoic acid) is approved for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle, which (section 8.4) includes infants in the early neonatal period. Midazolam (1% benzyl alcohol) is indicated for sedation of infants and children in the intensive care unit as a 24 hour continuous infusion, and Diazepam (1.5% benzyl alcohol) is indicated for children in status epilepticus.

The history of pediatric benzyl alcohol toxicity in neonates is summarized in a 1983 publication by the American Academy of Pediatrics (Little et al). In 1982 two independent groups of investigators (Gershanik and Brown) concluded that intravascular infusion of flush solutions containing 0.9% benzyl alcohol caused what was coined “gaspings syndrome” characterized by severe metabolic acidosis, encephalopathy and respiratory depression that led to the death of 16 infants in neonatal intensive care units. Affected neonates had large amounts of benzyl alcohol and its metabolites in blood and urine; in both studies, the volumes of flush solutions the infants received was estimated, and the benzyl alcohol level assessed to be administered was 99-405 mg/kg/day, close to levels known to be toxic for a single infusion in the sensitive species (adult rat). As a result FDA, together with the CDC and AAP, “urged pediatricians and other personnel...not to use fluids preserved with benzyl alcohol...for newborn infants and not to use diluents with this preservative to reconstitute or dilute medications for infants.” The AAP recommendation stated that “for newborn infants, it may be preferable to avoid use of medications with preservatives whenever possible. However, the presence of benzyl alcohol as a preservative should not proscribe use of medications indicated for treatment of an infant.”

Since these recommendations, the Joint FAO/WHO expert committee on Food Additives has evaluated benzyl derivatives as part of an effort (initiated in 2001) to provide scientific advice to Member States of the two organizations with respect to food regulations and control. These established “acceptable daily intakes” (ADIs) for these and other products, which included a range of 0-5 mg/kg/day for benzoic acid equivalents. No change was made to this recommendation during the last update in 2010.

In 2010, DHP consulted DPMH with regard to proposed language for benzyl alcohol-containing heparin formulations (for consistency across heparin products). DPMH reviewed the data above (with the exception of the FAO/WHO recommendations) and recommended:

- **W&P:**

Reference ID: 4088407 **Highlights:** *Benzyl Alcohol Toxicity: Preservative-free formulation recommended for*

neonates and infants. (5.2)

- **5.2 Benzyl Alcohol Toxicity**
  - *Preservative-free HEPARIN SODIUM INJECTION, when available, is recommended for use in neonates and infants. The preservative benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients [see Use in Specific Populations (8.4)].*
- The inclusion of “use in specific populations in the highlights”:
  - *Pregnancy: Preservative-free formulation recommended. Limited human data in pregnant women. (8.1)*
  - *Nursing Mothers: Preservative-free formulation recommended. Caution should be exercised when administered to a nursing woman. (8.3)*
  - *Pediatric Use: Preservative-free formulation recommended in neonates and infants. Dosing recommendations based on clinical experience. (2.4, 8.4)*

- **D&A as follows:**

## **2 DOSAGE AND ADMINISTRATION**

### **2.4 Pediatric Use**

*Preservative-free HEPARIN SODIUM INJECTION, when available, is recommended for use in neonates and infants*

- **8 Use in Specific Populations:**

- **8.1 Pregnancy:** *If available, preservative-free HEPARIN SODIUM INJECTION is recommended when heparin therapy is needed during pregnancy. There are no known adverse outcomes associated with fetal exposure to the preservative benzyl alcohol through maternal drug administration; however, the preservative benzyl alcohol can cause serious adverse events and death when administered intravenously to neonates and infants [see Use in Specific Populations (8.4)]*
- **8.3 Nursing Mothers:** *If available, preservative-free HEPARIN SODIUM INJECTION is recommended when heparin therapy is needed during lactation. Due to its large molecular weight, heparin is not likely to be excreted in human milk, and any heparin in milk would not be orally absorbed by a nursing infant. Benzyl alcohol present in maternal serum is likely to cross into human milk and may be orally absorbed by a nursing infant. Exercise caution when administering Heparin Sodium Injection to a nursing mother [see Use in Specific Populations (8.4)].*
- **8.4 Pediatric Use:** *Preservative-free HEPARIN SODIUM INJECTION, when available, is recommended for use in neonates and infants. The preservative benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients. The “gasp syndrome,” (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth weight infants. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse.*

*Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the*

*“gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.*

Thus, the use of a benzyl alcohol containing formulation in a product approved for pediatric use is not unprecedented. However, the data in the literature regarding benzyl alcohol toxicity in children should inform labeling to mitigate this potential risk, especially since the current non-benzyl alcohol containing formulation is available. It is noted that that the use of the benzyl alcohol containing preparation does bring with it the advantage of bag changes with substantially lower frequency than with the current formulation (7 days vs 24-48 hours), and that this should theoretically decrease the risk of infection, which is increased by more frequent access to a central line. All of these factors must be taken into account when making a benefit-risk assessment regarding the new formulation.

The Applicant calculates the amount of benzyl alcohol expect in the new formulation to be equivalent to  $\leq 5$  mg/kg/day for patients weighing 22 kg or more. This has been confirmed by this reviewer:

The addition of bacteriostatic saline to blinatumomab infusion solution will result in a concentration of 0.74% (7.4 mg/mL) of benzyl alcohol. Since the proposed infusion rate for this administration time is 0.6mL/hour, this translates into  $0.6 \times 24 = 14.4$  mL/day, which is  $(14.4\text{mg} \times 7.4\text{mL}) 106.56$  mg/day of benzyl alcohol. The lowest weight for which this amount is 5 mg/kg or less is  $106.56/5 = 21.3$  kg.

***Reviewer comment: The other benzyl alcohol-containing products which have labeling in PLR format are heparin sodium and Ferrlecit. Both have a more general precaution regarding avoidance of use in neonates and infants, but do not specify a specific weight cut-off for use; both contain the sentence (based on published literature on the subject) that “the minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known.” The current PI includes this statement as well (section 5.12). The more conservative 22 kg cut-off does not present safety concerns, and given the WHO ADI recommendations that doses of more than 5mg/kg/day should not be given, appears reasonable, especially given the inclusion of the sentence above regarding lack of data as to what the minimum amount that can cause toxicity. The sentence that follows in section 5.12, namely “(b) (4),” might be confusing, as the 22 kg cut-off- the 50<sup>th</sup> percentile for a 6 year old boy or a 6.5 year old girl- is much higher than that expected in infancy, (b) (4). The extra precaution for infants, the age group in which the toxicity has been best well-characterized (and in which it was initially discovered) appears to outweigh the potential for confusion. Another proposed sentence, however, regarding (b) (4) (b) (4) appears extraneous and should be removed, as it essentially contradicts the previous sentence regarding data that are unknown.***

***Also, the proposed label has multiple statements at multiple locations and does not appear to effectively convey the proposed message.***

***Another source of potential confusion is the difference in weight thresholds for dosing (45 kg) vs 7 day infusion (22 kg). These need to be clearly distinguished in labeling.***

***At the labeling meetings, changes were made to ensure consistency between the warnings and precautions concerning benzyl alcohol-containing products, as well as the reference to the above toxicities in section 8.4.***

***In response to the annotated PI sent to the applicant, they pointed out that the use of the word “(b) (4)” might be confusing, as the human factors study showed that some users used the (b) (4). It is noted that as proposed, the sentence “use preservative-free saline for patients weighing less than 22 kg” in the W&P section of the highlights renders the statement uninterpretable. If the word (b) (4) is not included, the bullet must be changed such that it is clear that what is being referenced is the saline used to prepare the blinatumomab.***

With regard to the data/information to confirm that benzyl alcohol does not affect the physiological disposition of blinatumomab, the applicant essentially re-submitted the data initially submitted in the briefing package for the meeting referred to above. They state that blinatumomab is cleared via proteolysis, and then rapidly eliminated, with minimal renal excretion (0.2% of excreted unchanged blinatumomab, at the 60 mcg/m<sup>2</sup>/day dose) and a mean terminal elimination half-life of approximately 2 hours. Benzyl alcohol is rapidly and completely oxidized to benzoic acid, which is conjugated with glycine (liver) and then excreted in the urine, mostly as hippuric acid (≥80%; <20% is excreted as benzoyl glucuronide). Seventy five to one hundred percent of the hippuric acid is cleared within 6 hours; it is completely cleared within 2-3 days. They thus state that benzoyl alcohol is not expected to affect blinatumomab exposure in vivo. They have submitted in vitro data showing that concentrations of blinatumomab were stable in the presence of benzyl alcohol.

***Reviewer comment: The applicant has not submitted additional data confirming the lack of a benzyl alcohol effect on the physiologic disposition of blinatumomab beyond what was initially submitted in the meeting package.***

***One known potential effect benzyl alcohol could have on proteins is induction of aggregation in a concentration, temperature and time dependent manner (Chi 2012). This would be addressed and detected, however, by the CMC data provided in the submission.***

***Ultimately, whether the data submitted have adequately addressed the above concern regarding disposition is deferred to the CMC reviewer. The CMC team has recommended approval.***

**Regulatory Recommendation:** From a clinical standpoint, I recommend approval of this supplement for the preparation of Blincyto diluted in bacteriostatic saline in an IV bag for 7-day administration. Refer to the final PI for specific labeling recommendations.

#### **References:**

Brown, P. Treatment of infant leukemias: challenge and promise. *ASH Education Book* (2013) 1, 596-600; doi: 10.1182/asheducation-2013.1.596.

Kotecha RS, Gottartdo NG, Kees UR and Cole CH, The evolution of clinical trials for infant acute lymphoblastic leukemia. *Blood Cancer Journal* (2014) 4, e200; doi:10.1038/bcj.2014.17.

Little GA et al. Benzyl Alcohol: Toxic Agent in Neonatal Units. *Pediatrics* 1983;72;356.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AVIVA C KRAUSS  
04/24/2017

DONNA PRZEPIORKA  
04/24/2017

I concur with the primary reviewer's recommendation for approval of the final negotiated changes in the prescribing information in this supplement.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125557Orig1s007**

**MICROBIOLOGY/VIROLOGY REVIEW(S)**

Center for Drug Evaluation and Research  
Office of Pharmaceutical Quality  
Office of Process and Facilities  
Division of Microbiology Assessment

## PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

**REVIEWER:** Jessica Hankins, Ph.D.  
**ACTING QAL:** Dupeh Palmer, Ph.D.

BLA: 125557/7  
Applicant: Amgen  
US License Number: 1080  
Submission Reviewed: Prior approval supplement (PAS) to support the addition of 0.9% benzyl alcohol as a preservative to blinatumomab infusion bags.  
Product: blinatumomab (Blincyto)  
Indication: Treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)  
Dosage Form: Lyophilized powder for solution, intravenous infusion (35 mg)  
Manufacturing Site: (b) (4)  
FDA Receipt Date: December 1, 2017  
Action Date: June 1, 2017

### Conclusion and Approvability Recommendation

The Prior Approval Supplement (PAS) was reviewed from a product quality microbiology perspective and is recommended for approval.

### Product Quality Microbiology Assessment

**Drug Product Quality Microbiology Information Reviewed**

Sequence	Submission date	Description
0091	December 1, 2016	PAS

0110	April 17, 2017	IR Response
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## **Module 3.2**

### **P.2.5 Microbiological Attributes of Blinatumomab Infusion Solution Containing Benzyl Alcohol**

#### Study Design

A study was conducted to evaluate the ability of the blinatumomab infusion solution containing benzyl alcohol to support the growth of various microorganisms. Infusion bags (100 mL) were prepared with normal saline, benzyl alcohol (final concentrations of 0%, 0.5%, 0.6%, and 0.74% w/v), IV solution stabilizer (1:50 dilution), and blinatumomab at a final concentration of 1900 ng/mL. The sponsor noted that the concentration of the drug product (DP) represents the amount required for a 7-day continuous infusion at a dose of 28 µg/day.

Infusion bags containing each concentration of benzyl alcohol were spiked with challenge microorganisms to a final concentration of ~ 100 colony forming units (CFUs)/mL. The following challenge organisms were used in the test:

- *Escherichia coli*
- *Pseudomonas aeruginosa*
- *Enterobacter cloacae*
- *Staphylococcus aureus*
- *Micrococcus luteus*
- *Candida albicans*

The infusion bags spiked with the challenge organisms were incubated at 20-25°C and samples were taken at Day 0, Day 4, Day 8, Day 10, Day 12, and Day 14. For each sample, CFUs/mL were determined in duplicate using membrane filtration followed by plating onto Trypticase Soy Agar (TSA) or Sabouraud Dextrose Agar (sequence 0110). The growth conditions for the challenge organisms are shown in the table below (sequence 0110).

Table 1.

Organism	Medium	Temperature	Growth Time	Recovery Time
<i>Escherichia coli</i>	TSA <sup>a</sup>	30-35°C	18-24 hours	2-5 days
<i>Pseudomonas aeruginosa</i>	TSA <sup>a</sup>	30-35°C	18-24 hours	2-5 days
<i>Enterobacter cloacae</i>	TSA <sup>a</sup>	30-35°C	18-24 hours	2-5 days
<i>Staphylococcus aureus</i>	TSA <sup>a</sup>	30-35°C	18-24 hours	2-5 days
<i>Micrococcus luteus</i>	TSA <sup>a</sup>	30-35°C	18-24 hours	2-5 days
<i>Candida albicans</i>	SABDEX <sup>b</sup>	20-25°C	42-54 hours	2-5 days

<sup>a</sup> Trypticase Soy Agar  
<sup>b</sup> Sabouraud Dextrose Agar

*Reviewer comment: The sponsor indicated in sequence 0110 that the challenge organisms were chosen due to a recommendation from the Agency during the original filing for the blinatumomab BLA. Human pathogens commonly associated with nosocomial infections were*

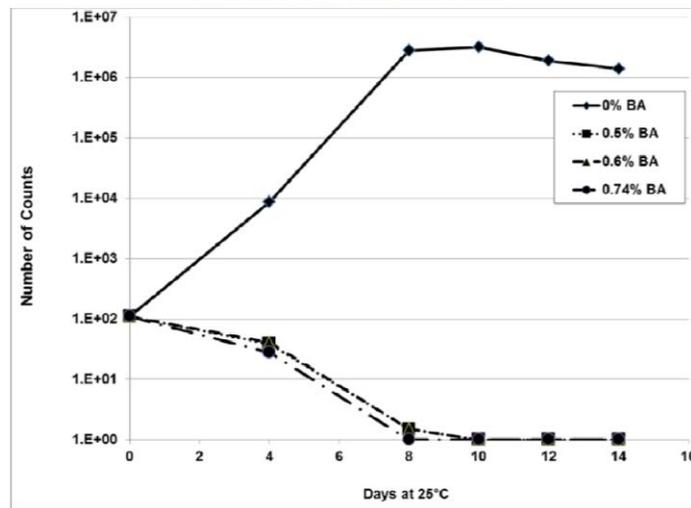
selected in alignment with Agency advice; therefore, *Aspergillus braziliensis* was replaced with three additional bacterial commonly associated with such infections.

Results

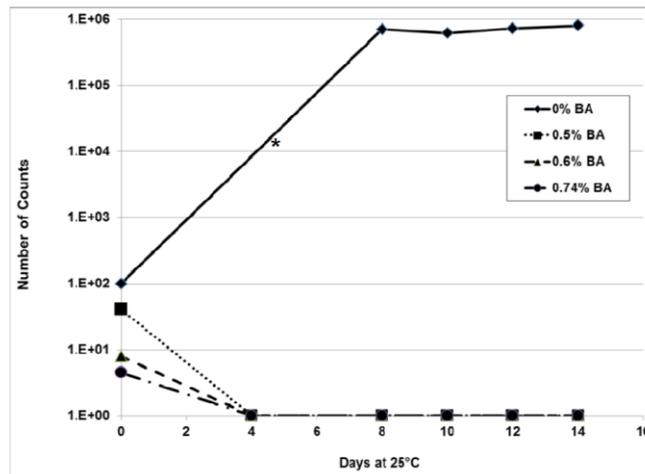
Gram-negative bacteria

In the presence of 0.5%, 0.6%, and 0.74% benzyl alcohol, the number of CFUs/mL for each challenge organism decreased over time. The decrease was observed at the Day 4 time point. The data is summarized in the figures shown below.

**Figure 1. Growth of *E. coli* in Blinatumomab Infusion Solution Containing Benzyl Alcohol**

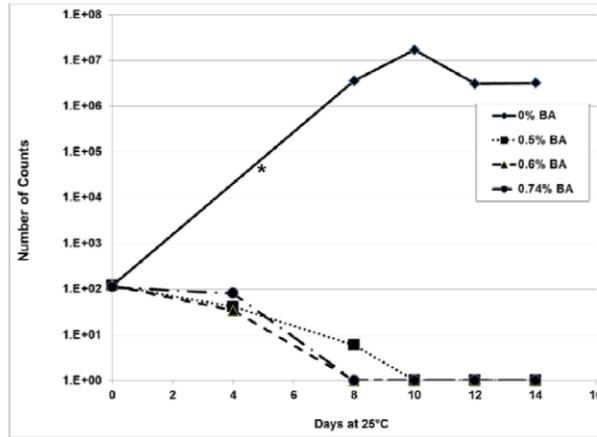


**Figure 2. Growth of *P. aeruginosa* in Blinatumomab Infusion Solution Containing Benzyl Alcohol**



\* The number of colonies after 4 days in 0% benzyl alcohol was too numerous to count, and is not represented in the figure.

Figure 3. Growth of *E. cloacae* in Blinatumomab Infusion Solution Containing Benzyl Alcohol



\* The number of colonies after 4 days in 0% benzyl alcohol was too numerous to count, and is not represented in the figure.

Gram-positive bacteria

Neither *S. aureus* nor *M. luteus* grew in the drug product or in the drug product with benzyl alcohol. Overall, the number of CFUs decreased throughout the 14-day incubation period; however, the CFUs decreased more readily in blinatumomab containing benzyl alcohol as shown in the figures below.

Figure 4. Growth of *S. aureus* in Blinatumomab Infusion Solution Containing Benzyl Alcohol

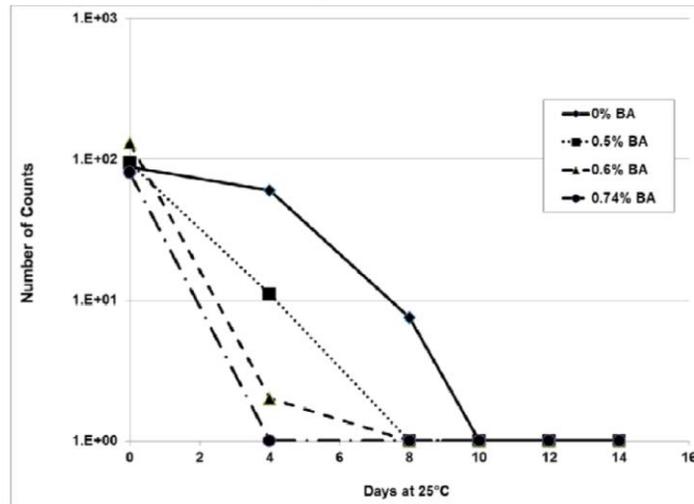
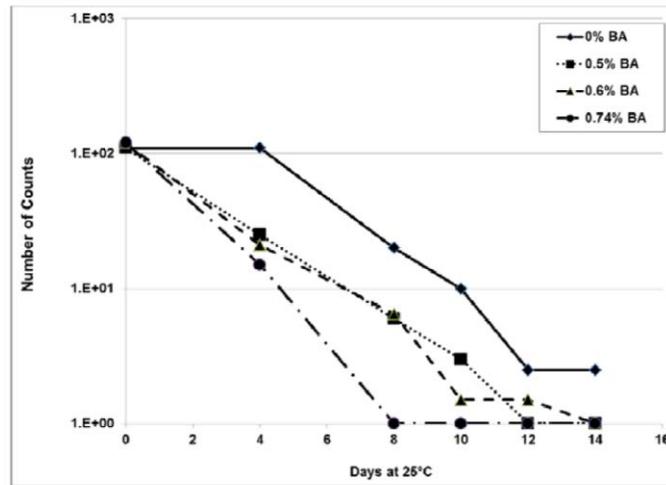


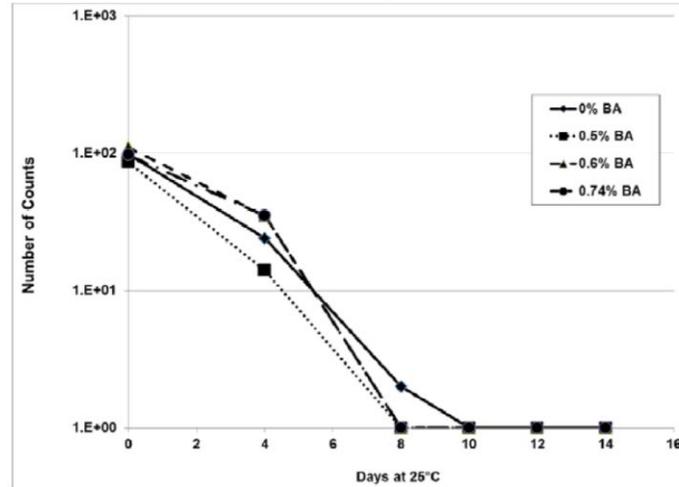
Figure 5. Growth of *M. luteus* in Blinatumomab Infusion Solution Containing Benzyl Alcohol



### Yeast

*C. albicans* did not grow in the blinatumomab infusion solution with or without benzyl alcohol. The results are shown in the figure below.

Figure 6. Growth of *C. albicans* in Blinatumomab Infusion Solution Containing Benzyl Alcohol



**Reviewer comment:** The blinatumomab infusion solution without benzyl alcohol supported the growth of *E. coli*, *E. cloacae*, and *Pseudomonas*. However, when 0.5%, 0.6%, or 0.74% benzyl alcohol were added to the blinatumomab infusion solution, the CFUs decreased over time for these Gram-negative organisms. The infusion solution without benzyl alcohol was not growth promoting for the Gram-positive organisms tested or for *C. albicans*. Additionally, no increase

*in growth was observed for these organisms when benzyl alcohol was added to the infusion solution.*

SATISFACTORY

### **Conclusion**

- I. The BLA supplement was reviewed from a product quality microbiology perspective and is recommended for approval.
- II. Product quality aspects other than microbiology should be reviewed by OBP.
- III. No inspection follow-up items were identified.

### **Drug Product Information Requests**

1. We note that each infusion solution was inoculated with approximately 100 CFUs/mL of each organism and that the CFUs/mL for each sample was determined by membrane filtration. However, the incubation conditions (media and temperature used) for each organism was not provided. Update section 3.2.P.2.5 with this information. Additionally, justify why a mold such as *Aspergillus brasiliensis* was not *used* in your study.

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/s/  
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JESSICA V HANKINS  
04/25/2017

DUPEH G Palmer-Ochieng  
04/25/2017

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125557Orig1s007**

**OTHER REVIEW(S)**

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** 4/18/17

**To:** Kristopher Kolibab, Regulatory Project Manager  
Division of Hematology Products (DHP)

**From:** Rachael Conklin, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** Comments on draft labeling (Package Insert, Carton/Container Labeling, Medication Guide) for BLINCYTO (blinatumomab) for injection, for intravenous use  
BLA 125557, S-007

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In response to your labeling consult requests dated December 5, 2016 we have reviewed the draft Package Insert for BLINCYTO (blinatumomab) for injection, for intravenous use (Blincyto) that includes updates based on S-007. This review is based upon the version of the draft PI and Med Guide e-mailed to OPDP on April 4, 2017 and the Carton/Container labeling accessed from the share drive on April 18, 2017.

We acknowledge that this is a supplement for an approved product; however, some of our comments included within this review apply to existing sections of the labeling that are already approved.

If you have any questions, please contact Rachael Conklin at (240) 402-8189 or [Rachael.Conklin@fda.hhs.gov](mailto:Rachael.Conklin@fda.hhs.gov).

**PI**

<b><u>Section</u></b>	<b><u>Statement from Draft (if applicable)</u></b>	<b><u>OPDP Comment</u></b>
<b>17 Patient Counseling Information</b>		OPDP recommends revising this section to include the pertinent counseling information regarding pregnancy, lactation, and contraception from sections 8.1, 8.2, and 8.3 and to include counseling information regarding immunization (5.11)

**Med Guide**

OPDP acknowledges and concurs with the April 7, 2017 review of the medication guide by the Division of Medical Policy Programs (DMPP) and has no additional comments on the medication guide at this time.

**Carton/Container Labeling**

OPDP does not have any comments on the carton and container labeling at this time.

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/s/  
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RACHAEL E CONKLIN  
04/18/2017

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: April 7, 2017

To: Ann Farrell, MD  
Director  
**Division of Hematology Products (DHP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Susan Redwood, MPH, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: Focused Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): BLINCYTO (blinatumomab)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: BLA 125557

Supplement Number: S-007

Applicant: Amgen Inc.

## **1 INTRODUCTION**

On December 1, 2016, Amgen, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS)-Labeling to their approved Biologics License Application (BLA) 125557/S-007 for BLINCYTO (blinatumomab) for injection. In S-007, the Applicant proposes updates to the Prescribing Information (PI) and Medication Guide (MG) to incorporate new admixing instructions to prepare single, 7-day BLINCYTO infusion bags in conjunction with Bacteriostatic 0.9% Sodium Chloride, USP (containing 0.9% benzyl alcohol) as preservative.

BLINCYTO (blinatumomab) for injection received Accelerated Approval on December 3, 2014 and is indicated for the treatment of Philadelphia chromosome negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Hematology Products (DHP) on December 5, 2016 for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG) for BLINCYTO (blinatumomab) for injection.

## **2 MATERIAL REVIEWED**

- Draft BLINCYTO (blinatumomab) for injection MG received on December 1, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on April 4, 2017.
- Draft BLINCYTO (blinatumomab) for injection Prescribing Information (PI) received on December 1, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on April 4, 2017.

## **3 REVIEW METHODS**

In our focused review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

## **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

## **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our focused review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/  
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SUSAN W REDWOOD  
04/07/2017

BARBARA A FULLER  
04/07/2017

LASHAWN M GRIFFITHS  
04/07/2017

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**HUMAN FACTORS LABEL COMPREHENSION AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** March 14, 2017

**Requesting Office or Division:** Division of Hematology Products (DHP)

**Application Type and Number:** BLA 125557/S-007

**Product Name and Strength:** Blincyto  
(blinatumomab)  
For Injection, 35 mcg per vial

**Product Type:** Combination (drug + stabilizing solution)

**Rx or OTC:** Rx

**Applicant/Sponsor Name:** Amgen

**Submission Date:** December 1, 2016

**OSE RCM #:** 2016-2744

**DMEPA Primary Reviewer:** Nicole Garrison, PharmD, BCPS

**DMEPA Team Leader:** Hina Mehta, PharmD

**DMEPA Acting Associate Director:** Mishale Mistry, PharmD, MPH

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## 1 REASON FOR REVIEW

The Division of Hematology Products (DHP) requested DMEPA evaluate the Labeling Comprehension Study results and Prescribing Information (PI) submitted on December 1, 2016, for BLA 125557/S-007, Blincyto (blinatumomab) to ensure the intended user population is able to understand the preparation of the product. The applicant submitted a Prior Approval Supplement, which proposes the addition of admixing instructions for preparation of a single 7 day continuous infusion. This study was conducted to evaluate proposed changes to the instructions in the PI for reconstitution and preparation of Blincyto to allow for an infusion of 7 days using a preservative.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

### 3.1 HUMAN FACTORS STUDY:

#### 3.1.1 Methodology:

Amgen conducted a summative label comprehension study for the revised reconstitution information in the Blincyto Prescribing Information (PI). DMEPA reviewed methodology for the label comprehension study on August 11, 2016<sup>a</sup> and had some recommendations on the order

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<sup>a</sup> Garrison, N. Human Factors Comprehension Review (NDA IND 100135). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Aug 11. 31 p. OSE RCM No.: 2015-2129-1.

and format of the comprehension questions, categorization of tasks, and the moderator's script, which were communicated to the applicant. The Applicant addressed all of our recommendations prior to conducting the label comp study. We confirmed that the Applicant has addressed all of comments in the summative study results.

### **3.1.2 Human factors label comprehension study results**

With regard to the results of the label comprehension, a total of 14 errors occurred during essential and safety critical tasks by 4 out of 15 total participants (See Appendix C for detailed errors that occurred in the Study). It should be noted that of the 14 errors, 11 were committed by two of those 4 participants.

Three types of errors occurred:

- Error in determining the correct starting IV bag solution volume (n =6)
- Error in determining the correct volume of IV Stabilizing Solution (IVSS) to transfer (n =3)
- Error in determining the correct volume of reconstituted drug product to transfer (n =5)

#### **Error in determining the correct starting IV bag solution volume (n =6)**

Six errors occurred in three participants who determined the incorrect starting IV bag volume. We note the number of errors is more than participants because each participant was asked to complete 4 different scenarios.

- One participant determined to transfer 262.5 mL (scenario 2) and 261.9 mL (scenario 4) of 0.9% NaCl solution rather than the required 270 mL into the IV bag. The participant misinterpreted the 270 mL starting volume given in the PI as the volume of a fully prepared bag at the start of the infusion, and determined to subtract transfer volumes of IVSS and drug product in order to calculate the initial 0.9% NaCl solution volume. During the scenario performance, the participant acknowledged the PI's instructions to add 270 mL of 0.9% NaCl solution, and did not see any instruction to adjust that volume. Since the participant acknowledged his actions were not based on instructions from the PI, we determined this error was not related to the labels and labeling of this product. Thus no further labeling changes are warranted.
- One participant determined to transfer 90 mL of bacteriostatic NaCl solution into the IV bag and QS to 110 mL with 0.9% NaCl solution rather than transfer the required 270 mL of 0.9% NaCl solution for doses to be infused over 24 hours (scenario 2 and 4). The participant admitted to skipping over sections (b) (4) (Administration and Preparation of 24 hour infusion) in the PI and while reading the 'Highlights' section of the PI, stopped reading prior to reaching the parentheticals containing section numbers associated with the various possible infusion durations. Additionally, the participant looked only for the administration section, as she typically does at work. When she saw the "Administration" heading in (b) (4), she assumed all relevant instructions could be found below in subsequent passages. Since the participant's actions were based on her previous experiences, the Applicant considered negative transfer to have contributed to

this error. However, we recommend making revisions to the Highlights and the Dosage and Administration section of the PI, to inform users that volumes of Blinycto differ based on the duration of the infusion.

- Another participant determined to transfer 270 mL of 0.9% NaCl solution into 7 separate 24-hour IV bags for a 7-day infusion (scenario 1), rather than transfer the required 90 mL of bacteriostatic NaCl solution and QS to 110 mL with 0.9% NaCl solution. During further investigation, the participant had read section (b) (4) (doses to be infused over 7 days), but had forgotten its existence prior to beginning the 1<sup>st</sup> scenario. During performance of the scenario, the participant folded the PI in half, which removed section (b) (4) from her visual field. She stated this would not occur in real life as she creates admixing templates for all possible doses directly from the PI. In a subsequent scenario (scenario 3), the same participant determined to transfer 11.3 mL of 0.9% NaCl solution, rather than the required 6.5 mL, into the IV bag containing 90 mL of bacteriostatic NaCl solution. While referencing the appropriate row in Table 5, the participant assumed the smaller of the two listed transfer volumes (6.5 mL) was the reconstituted drug product transfer volume and that the larger volume (11.3 mL) represented the volume of 0.9% NaCl solution required to QS the bag to a final volume of 110 mL. We acknowledge the participant knew the appropriate action to carry out as she discovered the error when asked to re-write the recipe during follow up discussion. In addition, she stated this would not occur in real life as she creates admixing templates for all possible doses directly from the PI. However, we recommend revising the PI to acknowledge informing users that volumes of Blinycto differ based on the duration of the infusion.

#### **Error in determining the correct volume of IVSS to transfer (n =3)**

Three errors occurred in two participants who determined the incorrect volume of IVSS to transfer to the IV bag. We note the number of errors is more than participants because each participant was asked to complete 4 different scenarios.

- One participant determined to transfer 2.2 mL of IVSS instead of 5.5 mL for doses to be infused over 24 hours in scenario 2 and 4. The participant admitted to skipping over sections (b) (4) (Administration and Preparation of 24 hour infusion) in the PI, and while reading the 'Highlights' section of the PI, stopped reading prior to reaching the parentheticals containing section numbers associated with the various possible infusion duration. Additionally, the participant looked only for the administration section, as she typically does at work. When she saw the "Administration" heading in (b) (4), she assumed all relevant instructions could be found below in subsequent passages. Since the participant's action was based on her previous experiences, the Applicant considered negative transfer to have contributed to this error. However, we recommend revising the Highlights and the Dosage and Administration section of the PI, to inform users that volumes of Blinycto differ based on the duration of the infusion.
- Another participant determined to transfer 5.5 mL of IVSS into 7 separate 24-hour IV bags for a 7-day infusion, rather than the required 2.2 mL of IVSSs required for a single 7-

day bag. During performance of the scenario, the participant folded the PI in half, which removed section (b) (4) from her visual field. We determined this error was not related to the labels and labeling of this product. Thus no further labeling changes are warranted.

### **Error in determining the correct volume of reconstituted drug product to transfer (n =5)**

Five errors occurred in three participants who did not determine the correct volume of reconstituted drug product to transfer to the IV bag for the prescribed dose. We note the number of errors is more than participants because each participant was asked to complete 4 different scenarios.

- One participant calculated to transfer 18 mL of reconstituted drug product into the IV bag by multiplying 3 mL by the number of vials (6) used to prepare the dose. The participant explained that a single dose is typically the entire contents of a vial and the drug product transfer volumes are typically equal to the volume of diluent added. In subsequent scenario, the participant realized that the transfer volume is not equal to the total reconstituted drug product volume. The proposed PI clearly states the volume of drug product to transfer per duration of the infusion. Thus, no further labeling recommendations are necessary.
- One participant determined the incorrect volume of drug product to transfer into the IV bag, using the transfer volumes given for 7-day infusions rather than 24-hour infusions (scenario 2 and 4). The participant admitted to skipping over sections (b) (4) (Administration and Preparation of 24 hour infusion) in the PI, and while reading the 'Highlights' section of the PI, stopped reading prior to reaching the parentheses containing section numbers associated with the various possible infusion duration. Additionally, the participant looked only for the administration section, as she typically does at work. When she saw the "Administration" heading in (b) (4), she assumed all relevant instructions could be found below in subsequent passages. Since the participant's action was based on her previous experiences, the Applicant considered negative transfer to have contributed to this error. Our review of the PI determined the volumes of reconstituted Blincyto required to prepare each dose is clearly labeled in a chart. Thus, no further labeling recommendations are warranted.
- Another participant determined to transfer 2.6 mL of reconstituted drug product into 7 separate 24-hour IV bags for a 7-day infusion, rather than the required 16.8 mL (scenario 1). During performance of the scenario, the participant folded the PI in half, which removed section (b) (4) from her visual field. Therefore, she prepared the dose using the 24-hour preparation instructions found in section (b) (4). In a subsequent scenario (scenario 3), the participant determined to transfer 6.5 mL of reconstituted drug product, rather than the required 11.3 mL. While referencing the appropriate row in Table 5, the participant assumed the smaller of the two listed transfer volumes (6.5 mL) was the reconstituted drug product transfer volume and that the larger figure (11.3 mL) represented the volume of 0.9% NaCl solution required to QS the bag to a final volume of 110 mL. We acknowledge the participant knew the appropriate action to carry out but forgot or did not do so. However, we recommend revising the Prescribing

Information to acknowledge in the differing starting volumes of Blincyto based on the duration of the infusion.

#### **4 LABELS AND LABELING**

In addition to the label comprehension study results, we reviewed the proposed PI to determine whether there were any areas that may be vulnerable to confusion that can lead to medication errors. The PI evaluated in the label comprehension study added preparation instructions for the 7 day infusion, in addition to the 24-hour and 48-hour infusions, and instructions for patients weighing at least 45 kg as well as patients weighing less than 45 kg. Most of the errors observed in the study can be attributed to participants not reading the entire PI, skipping sections of the PI, and performing their own calculations despite the having the information readily available in the PI. The Applicant proposed changes to the Dosage and Administration Section of the PI after the summative study as a result of recent changes made to the latest approved version of the PI and to include information on the use of benzyl alcohol as a preservative for patients weighing less than 45 kg. Additionally, the Applicant removed the requirement of an inline filter for patients receiving 7-day infusion duration. After review of the Applicant's changes and the study, we determined that additional changes were needed to the PI to inform the intended users that the preparation volumes of Blincyto differ based on the duration of the infusion.

In addition, we searched FAERS and identified 11 medication error cases (see Appendix E for detailed description of cases) relevant to this review as follows:

- Wrong technique of administration (n=5)
- Product preparation errors (n=6)

In the cases of wrong technique of administration, it was reported that Blincyto was administered at the incorrect rate or through an undedicated IV line. Root causes, contributing factors, or were patient outcomes were not reported. Although the errors occurred, the proposed PI is clear regarding the infusion rate. Thus, we do not recommend any changes to the labeling at this time. Another case reported the concurrent administration of Blincyto with 0.9% sodium chloride injection infusion via a Y site at 10 mL per hour. The physician recommended this as a precautionary measure in the event the patient developed an infusion related reaction, so the intravenous Blincyto dose could be stopped and the patient would continue to receive an infusion of 0.9% sodium chloride injection. The outcome of the event is unknown. After review of the proposed PI, the administration of Blincyto through a dedicated lumen is clear and bolded. Additionally, the error was related to instruction from the physician or medical practice and not a result of the labeling. Thus, we do not recommend any changes to the labeling at this time.

The cases involving product preparation errors reported instances where the Blincyto vial was reconstituted with the vial of IVSS, or the vial of IVSS was used to prepare more than 1 dose of Blincyto. Upon review of the proposed PI, we determined the PI, labels, and labeling was clear

that the vial of IVSS was a single dose vial and should be discarded after use. Thus, we do not recommend any changes to this information in PI, labels, or labeling at this time.

## 5 CONCLUSION & RECOMMENDATIONS

The results of the label comprehension study demonstrated that revisions were needed to the PI to ensure that the intended user population could comprehend the instructions for admixture for Blincyto. Some of the errors that occurred in the study were attributed to participant's lack of knowledge of the different preparation volumes required for each duration (e.g. 24 hour or 48 hour and 7 day) of Blincyto infusion. We identified areas in the proposed PI to increase clarity and prominence of the different preparation volumes required for each infusion duration of Blincyto. Notwithstanding additional data, the proposed changes are self-evident in addressing errors observed within the study. These changes to the user interface do not require an additional label comprehension study. See Section, 5.1, below, for our recommendations.

### 5.1 RECOMMENDATIONS FOR THE DIVISION

#### A. Prescribing Information

1. Highlights, Dosage and Administration
  - a. Special Administration and Preparation Considerations
    - i. We recommend adding a statement to inform the intended users that the starting volume of the IV bag is dependent upon the infusion duration.
2. Full Prescribing Information
  - a. Section 2.4 Special Preparation Considerations
    - i. We recommend to revise the statements to further highlight the specific infusion durations for Blincyto as follows:
      - a. For infusion over **24 or 48 hours** see **section 2.5**
      - b. For infusion over **7 days** using Bacteriostatic 0.9% Sodium Chloride, USP (containing 0.9% benzyl alcohol) see **section 2.6**. This option is available for patients weighing  $\geq 22$  kg. It is not recommended for the use in patients weighing  $\leq 22$  kg.
  - b. Section (b) (4) Preparation of Blincyto Infusion Bag for 24 or 48 Hour Infusion
    - i. In the beginning of the section, we recommend adding a statement to inform the intended users that the starting volume is dependent upon the infusion duration. We recommend this revision to mitigate the risk of preparations using the incorrect starting volume of the IV bag.
  - c. Section (b) (4) Preparation of Blincyto Infusion for 7-day Infusion

- i. In the beginning of the section, we recommend adding a statement to inform the intended users that the starting volume is dependent upon the infusion duration. We recommend this revision to mitigate the risk of preparations using the incorrect starting volume of the IV bag.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Blincyto that Amgen submitted on December 1, 2016.

<b>Table 2. Relevant Product Information for Blincyto</b>	
<b>Initial Approval Date</b>	December 3, 2014
<b>Active Ingredient</b>	Blinatumomab
<b>Indication</b>	For the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).
<b>Route of Administration</b>	Intravenous
<b>Dosage Form</b>	For Injection
<b>Strength</b>	35 mcg blinatumomab per vial
<b>Dose and Frequency</b>	<p>For patients at least 45 kg in weight</p> <ul style="list-style-type: none"> <li>In Cycle 1, administer 9 mcg/day for the first 7 days and 28 mcg/day on days 8-28.</li> <li>For subsequent cycles, administer 28 mcg/day on Days 1 through 28.</li> </ul> <p>For patients less than 45 kg in weight</p> <ul style="list-style-type: none"> <li>In Cycle 1, administer 5 mcg/m<sup>2</sup>/day for the first 7 days and increase dose to 15 mcg/m<sup>2</sup>/day on Days 8-28.</li> </ul> <p>For subsequent cycles, administer 15 mcg/m<sup>2</sup>/day on Days 1 through 28.</p>
<b>How Supplied</b>	Blinatumomab is supplied in a single-use vial containing a sterile, preservative-free, white to off-white lyophilized powder (35 mcg per vial). IV Solution Stabilizer is supplied in a 10 mL single use glass injection vial as a sterile, preservative free, clear to slightly yellow liquid concentrate
<b>Storage</b>	<p>Store blinatumomab and the IV Solution Stabilizer in the original package refrigerated at 2°C to 8°C (36°F to 46°F) and protect from light until time of use.</p> <p>Store and transport the prepared IV bag containing Blincyto solution for infusion at 2°C to 8°C (36°F to 46°F) conditions. Ship in packaging that has been validated to maintain temperature of the contents at 2°C to 8°C (36°F to 46°F). Do not freeze</p>

## APPENDIX B. PREVIOUS DMEPA REVIEWS

### B.1 Methods

On December 23, 2016, we searched the L:drive and AIMS using the terms, Blinatumomab to identify reviews previously performed by DMEPA.

### B.2 Results

Our search identified two previous proprietary name reviews<sup>b, c</sup> and eleven human factors protocol and labeling reviews<sup>d,e,f,g,h,i,j,k,l,m,n</sup>, which we confirmed that our previous recommendations were implemented or considered.

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<sup>b</sup> Gao, T. Proprietary Name Review for Blincyto (IND 100135). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 NOV 4. 23 p. RCM No.: 2013-1952.

<sup>c</sup> Vora, N. Proprietary Name Review for Blincyto (BLA 125557). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 NOV 13. 23 p. RCM No.: 2014-36966.

<sup>d</sup> Vora, N. Human Factors Protocol Review for Blincyto (IND 100135). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JUN 27.11 p. RCM No.: 2014-1127.

<sup>e</sup> Vora, N. Human Factors Results Review for Blincyto (IND 100135). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 AUG 6. 28 p. RCM No.: 2014-1622.

<sup>f</sup> Vora, N. Human Factors Protocol and Label and Labeling Memo for Blincyto (IND 100135 and BLA 125557). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 OCT 10. 15 p. RCM No.: 2014-1622-1.

<sup>g</sup> Vora, N. Human Factors Supplemental Study Results and Label and Labeling Memo for Blincyto ( BLA 125557). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 NOV 24. 5 p. RCM No.: 2014-1622-2.

<sup>h</sup> Vora, N. Human Factors Summary and Use Related Assessment Summary Report Memo for Blincyto (BLA 125557). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 JAN 8. 1 p. RCM No.: 2014-2526.

<sup>i</sup> Garrison, N. Human Factors Labeling Comprehension Review for Blincyto (IND 100135). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 OCT 21. 28 p. RCM No.: 2015-2129.

<sup>j</sup> Garrison, N. Human Factors Study Protocol Memo for Blincyto (IND 100135). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 NOV 25. 2 p. RCM No.: 2015-2129-1.

<sup>k</sup> Garrison, N. Human Factors Label Comprehension Study and Labeling Review for Blincyto (BLA 125557/S-005). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUL 11. 32 p. RCM No.: 2016-579.

<sup>l</sup> Garrison, N. Human Factors Label Comprehension Study Protocol Review for Blincyto (IND 100135). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 AUG 11. 31 p. RCM No.: 2015-2129-1.

<sup>m</sup> Garrison, N. Review of Revised Label and Labeling for Blincyto (BLA 125557/S-005). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 AUG 08. 2 p. RCM No.: 2016-579-1.

<sup>n</sup> Garrison, N. Review of Human Factors Protocol Comments for Blincyto (IND 100135). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 SEP 07. 2 p. RCM No.: 2015-2129-2.

## APPENDIX C. LABEL COMPREHENSION STUDY

### C.1 Deviations

The participants were provided with a corrected version of the PI, as the PI that was included in the Summative Study Protocol contained typos. The corrections included:

- Page 1 of the PI, under Administration and Preparation sections, added parenthetical references to Section (b) (4) (7-day preparation) where only (b) (4) had been referenced
- Added text to section header (b) (4) to include “for 24 or 48 Hour Infusion”
- Corrected error in section (b) (4), with reference to section (b) (4), instead of section (b) (4)
- Added text to section header (b) (4) to include “for 7 Day Infusion”

### C.2 Results

Overall, 73% of participants (11 out of 15) completed all scenarios without committing any use error resulting in failure, close calls, operational difficulties or intentional misuse on any essential and/or safety critical steps. The remaining 27% of participants (4 out of 15) committed a total of 14 essential and/or safety critical steps use errors. It should be noted that 11 of the 14 use errors were committed by 2 participants.

**Table 4: Essential/Safety-Critical Steps**

Step Description	Success Criteria	Essential/ Safety- Critical	# of Use Errors	Performance Rate*
Verify prescription for all doses.	Participant correctly identifies the dosage and infusion duration and acknowledges the appropriate section in the PI.	E and SC	0	<b>100%</b> 15/15
Determine correct starting volume and transfer to empty IV bag:  <ul style="list-style-type: none"> <li>• Normal saline solution for doses to be infused over 24/48 hours</li> </ul> <i>or</i> <ul style="list-style-type: none"> <li>• Bacteriostatic saline solution and normal saline solution for doses to be infused over 7 days</li> </ul>	Participant correctly identifies appropriate starting volume of:  <ul style="list-style-type: none"> <li>• Normal saline solution for doses to be infused over 24/48 hours</li> </ul> <i>or</i> <ul style="list-style-type: none"> <li>• Bacteriostatic saline solution and normal saline solution for doses to be infused over 7 days.</li> </ul>	E and SC	6	<b>80%</b> 12/15
Transfer correct volume of IVSS.	Participant identifies appropriate transfer volumes of IVSS.	E	3	<b>87%</b> 13/15
Reconstitute a vial of BLINCYTO with sWFI	Participant correctly identifies appropriate transfer volume of sWFI (demonstrates understanding that IVSS is not to be used for reconstitution).	E and SC	0	<b>100%</b> 15/15
Transfer reconstituted BLINCYTO to IV bag	Participant identifies the appropriate transfer volumes of reconstituted BLINCYTO.	E and SC	5	<b>80%</b> 12/15

\*Performance rate is defined as the percentage of participants that completed a given step without committing a use error, and does not include repeated use errors committed by the same participant in separate scenarios.

### Root causes of errors

In part, these errors were caused by an incomplete reading of the relevant sections and tables in the PI, and a slip involving accidental reference to the wrong table. Two participants did not recognize their errors, and repeated the same errors for each of the four scenarios.

**Table 5: Root Cause Analysis for IV Bag Solution Volume Errors**

Pp#	Observation	Root Cause
2	<p>Participant did not identify appropriate volume of 0.9% NaCl solution to add to the IV bag for doses to be infused over 24 hours.</p> <p>(2 use errors: Scenarios 2, 4)</p> <p>Participant determined to transfer 262.5 mL (scenario 2) and 261.9 mL (scenario 4) of 0.9% NaCl solution rather than the required 270 mL into the IV bag.</p> <p>Scenario 2: <u>15 mcg/m<sup>2</sup>/day over 24 hours</u> (&lt;45 kg)</p> <p>Scenario 4: <u>28 mcg/day over 24 hours</u> (&gt;45 kg)</p>	<p><b>Cognition:</b> Incorrect mental model</p> <p>Participant misinterpreted the 270 mL starting volume given in the PI as the volume of a fully prepared bag at the start of infusion, and determined to subtract transfer volumes of IVSS and DP in order to calculate the initial 0.9% NaCl solution volume. This mental model was reinforced during the previous 7-day infusion admixing scenario, where initial 0.9% NaCl solution volume was dependent on the transfer volumes of IVSS and reconstituted DP.</p> <p>Note: During scenario performance participant acknowledged the PI's explicit instruction to add 270 mL of 0.9% NaCl solution, and did not see any instruction to adjust that volume. After expressing confusion, participant stated she would have double-checked and called the manufacturer.</p>
8	<p>Participant did not identify appropriate volume and type of NaCl solution for doses to be infused over 24 hours.</p> <p>(2 use errors: Scenarios 2, 4)</p> <p>Participant determined to transfer 90 mL of bacteriostatic NaCl solution into the IV bag and QS to 110 mL with 0.9% NaCl solution rather than transfer the required 270 mL of 0.9% NaCl solution for doses to be infused over 24 hours.</p> <p>Scenario 2: <u>15 mcg/m<sup>2</sup>/day over 24 hours</u> (&lt;45 kg)</p> <p>Scenario 4: <u>28 mcg/day over 24 hours</u> (&gt;45 kg)</p>	<p><b>Cognition:</b> Negative transfer of training, Terminal search</p> <p>Participant did not recognize the existence of separate dedicated sections for the preparation of doses infused over 24/48 hours and over 7 days. During familiarization, she skipped over sections (b) (4) and while reading the 'Highlights' section of the PI, stopped reading prior to reaching the parentheticals containing section numbers associated with the various possible infusion durations (Terminal search).</p> <p>Additionally, participant looked only for the administration section, as she typically does at work. When she saw the "Administration" heading in (b) (4) she assumed all relevant instructions could be found below in subsequent passages and tables (Negative transfer of training, Terminal search).</p>

		Note: Participant was aware that she was referencing the 7-day infusion instructions for doses to be infused over 24 hours, but decided to proceed without seeking clarification. Participant also acknowledged reading the PI too quickly and skipping to the wrong place, and communicated that in real life it would be appropriate to read the entire PI.
14	<p>Participant did not identify appropriate volume and type of saline solution for dose to be infused over 7 days.</p> <p>(1 use error: Scenario 1)</p> <p>Participant determined to transfer 270 mL of 0.9% NaCl solution into 7 separate 24-hour IV bags for a 7-day infusion, rather than transfer the required 90 mL of bacteriostatic NaCl solution and QS to 110 mL with 0.9% NaCl solution.</p> <p>Scenario 1: <u>28 mcg/day over 7 days</u> (&gt;45 kg)</p>	<p><b>Cognition and Action:</b> Lapse, Commission</p> <p>Participant had read section (b) (4) doses to be infused over 7 days) during familiarization but had temporarily forgotten its existence prior to beginning her 1<sup>st</sup> scenario (Lapse). During the performance portion of that scenario, she removed section (b) (4) from her visual field when she folded the PI in half, and prepared 7 separate 24-hour bags using the 24-hour preparation instructions found in section (b) (4) (Commission).</p> <p>Note: In subsequent scenario participant unfolded the PI and rediscovered section (b) (4) and correctly prepared a 7-day infusion bag. Participant explained that her error would not have occurred in real life as she creates an admixing template for all possible doses directly from the PI before preparing her first infusion bag.</p>
14	<p>Participant determined the correct volume of bacteriostatic saline solution for a dose to be infused over 7 days but did not identify the appropriate volume of 0.9% NaCl solution to add to the bag.</p> <p>(1 use error: Scenario 3)</p> <p>Participant determined to transfer 11.3 mL of 0.9% NaCl solution, rather than the required 6.5 mL, into the IV bag containing 90 mL of bacteriostatic NaCl solution.</p> <p>Scenario 3: <u>15 mcg/m<sup>2</sup>/day over 7 days</u> (&lt;45 kg)</p>	<p><b>Cognition:</b> Incorrect mental model</p> <p>While referencing the appropriate row in Table 5, participant assumed the smaller of the two listed transfer volumes (6.5 mL) was the reconstituted DP transfer volume and that the larger figure (11.3 mL) represented the volume of 0.9% NaCl solution required to QS the bag to a final volume of 110 mL.</p> <p>Note: Participant discovered the error when asked to re-write her recipe card during follow up discussion. Participant explained that her error would not have occurred in real life as she creates an admixing template for all possible doses directly from the PI before preparing her first infusion bag.</p>

**Table 6: Root Cause Analysis for IVSS Transfer Volume Errors**

Pp#	Observation	Root Cause
8	<p>Participant identified an incorrect transfer volume of IVSS.</p> <p>(2 use errors: Scenarios 2, 4)</p> <p>Participant determined to transfer 2.2 mL of IVSS instead of 5.5 mL for doses to be infused over 24 hours.</p> <p>Scenario 2: <u>15 mcg/m<sup>2</sup>/day over 24 hours</u> (&lt;45 kg)</p> <p>Scenario 4: <u>28 mcg/day over 24 hours</u> (≥45 kg)</p>	<p><b>Cognition:</b> Negative transfer of training, Terminal search</p> <p>Participant did not recognize the existence of separate dedicated sections for the preparation of doses infused over 24/48 hours and over 7 days. During familiarization, she skipped over sections (b) (4) and stopped reading the 'Highlights' section prior to reaching the parentheticals containing section numbers associated with the various possible infusion durations (Terminal search).</p> <p>Additionally, participant looked only for the administration section, as she typically does at work. When she saw the "Administration" heading in (b) (4), she assumed all relevant instructions could be found below in subsequent passages and tables (Negative transfer of training, Terminal search).</p> <p>Note: Participant was aware that she was referencing the 7-day infusion instructions for doses to be infused over 24 hours, but decided to proceed without seeking clarification. Participant also acknowledged reading the PI too quickly and skipping to the wrong place, and communicated that in real life it would be appropriate to read the entire PI.</p>
14	<p>Participant identified an incorrect transfer volume of IVSS.</p> <p>(1 use error: Scenario 1)</p> <p>Participant determined to transfer 5.5 mL of IVSS into 7 separate 24-hour IV bags for a 7-day infusion, rather than the required 2.2 mL of IVSS required for a single 7-day bag.</p> <p>Scenario 1: <u>28 mcg/day over 7 days</u></p>	<p><b>Cognition and Action:</b> Lapse, Commission</p> <p>Participant had read section (b) (4) (doses to be infused over 7 days) during familiarization but had forgotten its existence prior to beginning her 1<sup>st</sup> scenario (Lapse). During the performance portion of that scenario, she folded the PI in half rendering section (b) (4) invisible and she prepared the dose using the 24-hour preparation instructions found in section (b) (4) (Commission).</p> <p>Note: In subsequent scenario participant unfolded the PI and rediscovered section (b) (4) and correctly</p>

Pp#	Observation	Root Cause
	(≥45 kg)	prepared a 7-day infusion bag. Participant explained that her error would not have occurred in real life as she creates an admixing template for all possible doses directly from the PI before preparing her first infusion bag.

Table 7: Root Cause Analysis for DP Transfer Volume Errors

Pp#	Observation	Root Cause
1	<p>Participant identified an incorrect transfer volume of reconstituted DP.</p> <p>(1 use error: Scenario 1)</p> <p>Participant determined to transfer 18 ml of reconstituted DP into the IV bag rather than the required 16.8 ml.</p> <p>Scenario 1: <u>28 mcg/day over 7 days</u> (&gt;45 kg)</p>	<p><b>Cognition:</b> Negative transfer of training</p> <p>Participant calculated 18 mL by multiplying 3 mL by the number of vials (6) used to prepare the dose. Participant explained that a single dose is typically the entire contents of a vial, and the DP transfer volume is typically equal to the volume of diluent added. Participant acknowledged seeing the instructions to add 16.8 mL and assumed that the final transferred volume was slightly lower than 18 due to the absorption of diluent by the DP powder.</p> <p>Note: In a subsequent scenario involving a dose that requires 5 vials, the large discrepancy between the stated transfer volume (11.3 mL) and his calculated transfer volume (15 mL) caused him to realize that the transfer volume is not equal to total reconstituted DP volume.</p>
8	<p>Participant identified an incorrect transfer volume of reconstituted DP.</p> <p>(2 use errors: Scenarios 2, 4)</p> <p>Participant determined the incorrect volume of DP to transfer into the IV bag, using the transfer volumes given for 7-day infusions rather than 24-hour infusions.</p> <p>Scenario 2: <u>15 mcg/m<sup>2</sup>/day over 24 hours</u> (&lt;45 kg)</p> <p>Scenario 4: <u>28 mcg/day over 24 hours</u></p>	<p><b>Cognition:</b> Negative transfer of training, Terminal search</p> <p>Participant did not recognize the existence of separate dedicated sections for the preparation of doses infused over 24/48 hours and over 7 days. During familiarization, she skipped over <a href="#">sections (b) (4)</a> and stopped reading the 'Highlights' section prior to reaching the parentheses containing section numbers associated with the various possible infusion durations (Terminal search).</p> <p>Additionally, participant looked only for the administration section, as she typically does at work. When she saw the "Administration" heading</p>

Pp#	Observation	Root Cause
	<p>(≥45 kg)</p>	<p>in (b) (4) she assumed all relevant instructions could be found below in subsequent passages and tables (Negative transfer of training, Terminal search).</p> <p>Note: Participant was aware that she was referencing the 7-day infusion instructions for doses to be infused over 24 hours, but decided to proceed without seeking clarification. Participant also acknowledged reading the PI too quickly and skipping to the wrong place, and communicated that in real life it would be appropriate to read the entire PI.</p>
14	<p>Participant identified an incorrect transfer volume of reconstituted DP.</p> <p>(1 use error: Scenario 1)</p> <p>Participant determined to transfer 2.6 mL of reconstituted DP into 7 separate 24-hour IV bags for a 7-day infusion, rather than the required 16.8 mL.</p> <p>Scenario 1: <u>28 mcg/day over 7 days</u> (≥45 kg)</p>	<p>Cognition and Action: Lapse, Commission</p> <p>Participant had read section (b) (4) doses to be infused over 7 days) during familiarization but had forgotten its existence prior to beginning her 1<sup>st</sup> scenario (Lapse). During the performance portion of that scenario, she folded the PI in half rendering section (b) (4) invisible and she prepared the dose using the 24-hour preparation instructions found in section (b) (4) Commission).</p> <p>Note: In subsequent scenario participant unfolded the PI and rediscovered section (b) (4) and correctly prepared a 7-day infusion bag. Participant explained that her error would not have occurred in real life as she creates an admixing template for all possible doses directly from the PI before preparing her first infusion bag.</p>
14	<p>Participant identified an incorrect transfer volume of reconstituted DP.</p> <p>(1 use error: Scenario 3)</p> <p>Participant determined to transfer 6.5 mL of reconstituted DP, rather than the required 11.3 mL.</p> <p>Scenario 3: <u>15 mcg/m<sup>2</sup>/day over 7 days</u> (&lt;45 kg)</p>	<p>Cognition: Incorrect mental model</p> <p>While referencing the appropriate row in Table 5, participant assumed the smaller of the two listed transfer volumes (6.5 mL) was the reconstituted DP transfer volume and that the larger figure (11.3 mL) represented the volume of 0.9% NaCl solution required to QS the bag to a final volume of 110 mL.</p> <p>Note: Participant discovered the error when asked to re-write her recipe card during follow up discussion. Participant explained that her error would not have occurred in real life as she creates an admixing template for all possible doses directly from the PI before preparing her first infusion bag.</p>

### User Needs Requirements Applicable to Supplemental Summative Study

The results are provided to help Amgen determine how well the product meets the identified user needs.

**Table 8: User Needs Requirements Applicable to Supplemental Summative Study**

Feature Number	Minimum Requirement	Success Criteria	Success Rate
UNR_02	The pharmacist can mix the prescribed dose using procedures that can be performed in pharmacy capable of aseptic compounding, but that may not be commonly used.	Participant correctly: <ol style="list-style-type: none"> <li>1. Verifies prescription for all doses,</li> <li>2. Identifies appropriate starting volumes of each type of saline solution for all doses,</li> <li>3. Demonstrates understanding that IVSS is not to be used for reconstitution,</li> <li>4. Identifies appropriate transfer volumes of IVSS,</li> <li>5. Identifies sWFI as the diluent to be used for reconstitution,</li> <li>6. Identifies appropriate transfer volumes of sWFI,</li> <li>7. Identifies appropriate transfer volumes of reconstituted DP.</li> </ol>	<b>73%</b> 11/15
UNR_12	The pharmacist must be able to identify the drug product and other items in the package in order to admix the prescribed IV drug solution correctly.	Participant correctly: <ol style="list-style-type: none"> <li>1. Demonstrates understanding that IVSS is not to be used for reconstitution,</li> <li>2. Identifies appropriate transfer volumes of IVSS,</li> <li>3. Identifies, sWFI as the diluent to be used for reconstitution,</li> <li>4. Identifies appropriate transfer volumes of sWFI,</li> <li>5. Identifies appropriate transfer volumes of reconstituted DP.</li> </ol>	<b>80%</b> 12/15

### **General Comprehension of Infusion Rate**

To further determine the general comprehension of the PI, participants were asked questions about the infusion rates required for each of the prepared doses from Scenarios 1-4. All answered these general comprehension questions correctly.

## Post-Test Questionnaire

Table 9: Post-Test Ratings

PI Post-Test Questionnaire	Frequency Count of Ratings*							Mean
	1	2	3	4	5	6	7	
1. The PI included all the information that I would expect.	0	1	0	0	1	3	10	6.3
2. The PI showed information clearly and effectively.	0	1	1	0	2	2	9	6
3. The PI was easy to understand.	0	1	1	0	1	6	6	5.9
4. The flow of information provided in the PI was easy to follow.	0	1	1	0	0	6	7	6

\*(1 = "Strongly Disagree", 7 = "Strongly Agree")

2 participants (Pp# 1 and 6) provided a total of 7 ratings of "3" or below, and reported the following rationales:

- Participant #1 provided ratings of "3" for statements 2, 3 and 4 because of the complexity of the admixing process.
- Participant #6 provided ratings of "2" for statements 1, 2, 3 and 4 because she expected that there would be more separation between the weight categories in the PI.

Overall, the average ratings for each item ranged from 5.9 to 6.3, suggesting that participants generally found their interaction with the PI to be positive.

### Post summative changes

The Applicant is implementing changes to the PI of Blincyto after the summative study as a result of recent changes made to the latest approved version of the PI and to include information on the use of benzyl alcohol as a preservative for patients weighing less than 45 kg. Additionally, the Applicant removed the requirement of an inline filter for patients receiving 7-day infusion duration.

## APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

### E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on February 8, 2016 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.<sup>o</sup>

<b>Initial FDA Receive Dates</b>	June 1, 2016 to January 31, 2017
<b>Product Name</b>	Blinicyto
<b>Product Active Ingredient</b>	Blinatumomab
<b>Event (MedDRA Terms)</b>	<i>Medication errors SMQ (narrow)</i>

### E.2 Results

Our search identified 17 cases, of which 11 described errors that needed to be evaluated further to understand whether they are relevant to this review. We excluded 6 cases because they described accidental exposure to the patient (n =1), intentional dose omission (n =2), dose omission due to device expulsion issue (n =1), no error was reported (n =1) and intentional overdose (n=1).

#### **Wrong technique of administration (n =5)**

- Four cases (FAERS case No. 13010751, 12440550, 12745199, and 12718403) reported instances where Blincyto was administered at an incorrect rate. In three of the cases, the IV bag was administered faster than recommended in the PI. Neither patient outcomes nor contributing factors were reported. Although the errors occurred, the proposed PI is clear regarding the infusion rate required based on the duration of the infusion. Thus, we do not recommend any changes to the labeling at this time.
- One case (FAERS case No. 13010728) reported a physician was concerned about infusion related reactions during the administration of Blincyto, so the patient received 0.9% sodium chloride injection infusion via a Y site at 10 mL. The physician wanted the 0.9% sodium chloride injection to infuse concurrently, so the Blincyto IV bag could be stopped and the sodium chloride injection could continue to run in the event the patient had an infusion related reaction. The outcome of the event is unknown. After review of the

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<sup>o</sup> The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

proposed PI, it is clear and bolded regarding the administration of Blincyto through a dedicated lumen. Additionally, the error was related to instruction from the physician and not a result of the labeling. Thus, we do not recommend any changes to the labeling at this time.

### **Product preparation error (n =6)**

- Two cases (FAERS case No. 12718370 and 12718445) reported incorrect reconstitution of the Blincyto vial with the vial of IVSS. One of the cases contributed the error to lack of familiarity with the process and reconstitution of Blincyto. The patient had received three hours of therapy with the improperly mixed Blincyto before the error was noticed and the IV bag was replaced. The outcome of the event was not reported. The second case did not report contributing factors or outcomes. In reconstitution steps of the PI, the following statement is bolded and underlined, “**Do not reconstitute Blincyto with IV Solution Stabilizer.**” Furthermore, the IVSS container label states in red font and capital letters, “NOT FOR DIRECT RECONSTITUTION OF BLINCYTO”. Thus, we do not recommend any changes to this information in PI at this time.
- Three cases (FAERS case No. 12718390, 12718466, and 12718375) reported instances in which the IVSS was used to prepare more than one dose of Blincyto. In one of the cases, it was reported that the facility ran out of the IVSS vials. It was implied that in reconstitution of the product, the facility used the IVSS vial more than once. No further details were provided in the case. In two of the cases, it was reported that the pharmacist was trying to maximize the amount of IVSS and minimize waste and therefore might use the IVSS vial to prepare more than one IV bag. The pharmacist knew there was 96 hour stability data, and wanted to prepare the Blincyto bags in advance and refrigerate them for 96 hours. Upon review of the proposed PI, users are instructed to discard the vial containing the unused IVSS. Additionally, the carton labeling states it is a single-use vial and to discard the unused portion. Thus, we do not recommend any changes to this information in PI at this time.
- One case (FAERS case No. 12718407) reported that the incorrect dose of Blincyto was prepared. The order was written to prepare a 28 mcg/day IV bag of Blincyto, however a 9 mcg/day IV bag was prepared in error. The patient received the incorrect dose of Blincyto. The pharmacist determined that the error would not affect the treatment, so they adjusted the dose and continued therapy. It was reported that the patient tolerated Blincyto well. The root cause of the error was not reported. Although this error occurred, the PI clearly states the dose preparation steps for each dose of Blincyto in a table format. Thus, we do not consider this error related to labeling of the product.

### **E.3 List of FAERS Case Numbers**

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

FAERS Case Number	Version	Manufacturer Control Number
13010751	1	US-AMGEN-USASP2016140419
12440550	1	US-AMGEN-USASP2016058733
12745199	1	US-AMGEN-USASP2016122869
12718370	2	US-AMGEN-USASP2016075290
12718375	2	US-AMGEN-USASP2016079148
12718390	2	US-AMGEN-USASP2016079330
12718403	2	US-AMGEN-USASP2016079471
12718407	2	US-AMGEN-USASP2016086022
12718445	2	US-AMGEN-USASP2016115579
12718466	2	US-AMGEN-USASP2016115644
13010728	1	US-AMGEN-USASP2016124790

#### E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>p</sup> along with postmarket medication error data, we reviewed the following Blincyto labels and labeling submitted by Amgen on December 1, 2016.

- A. Prescribing Information
- B. Instructions for Admixture used during the summative study
- C. Instructions for Admixture post summative study

### G.2 Label and Labeling Images

- A. Prescribing Information



uspi-vx-preserv-ar-20  
16-1129.doc

- B. Instructions for Admixture used during the summative study

**Table 2. For Patients Weighing Greater Than or Equal to 45 kg: Volumes to add to IV Bag**

<b>0.9% Sodium Chloride, USP (starting volume)</b>			270 mL
<b>IV Solution Stabilizer</b>			5.5 mL
<b>Dose</b>	<b>Infusion Duration</b>	<b>Infusion Rate</b>	<b>Reconstituted BLINCYTO</b>
9 mcg/day	24 hours	10 mL/hour	0.83 mL
	48 hours	5 mL/hour	1.7 mL
28 mcg/day	24 hours	10 mL/hour	2.6 mL
	48 hours	5 mL/hour	5.2 mL*

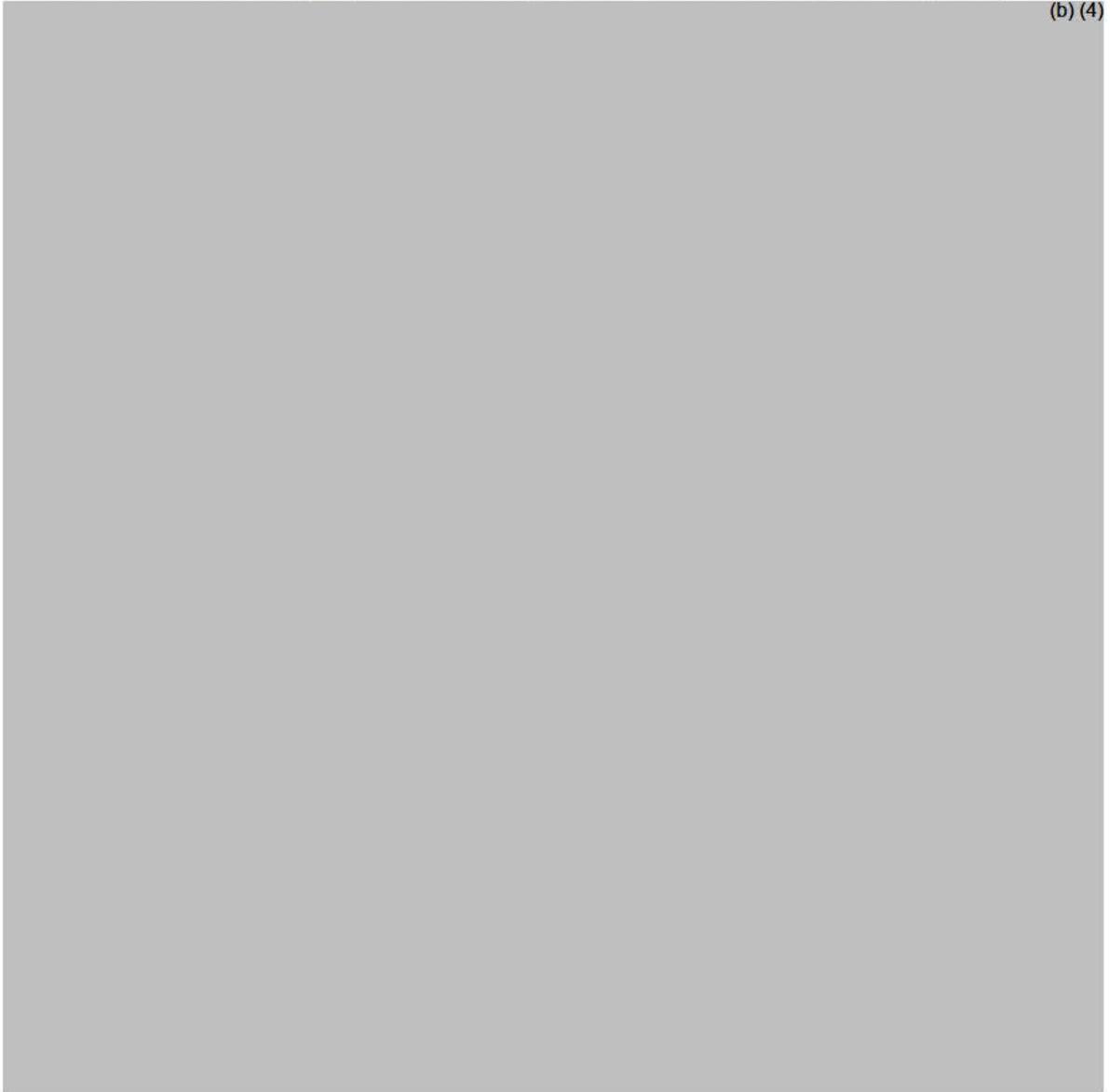
\* 2 packages of BLINCYTO are needed for preparation of 28 mcg/day dose infused over 48 hours at a rate of 5 mL/hour.

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<sup>p</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

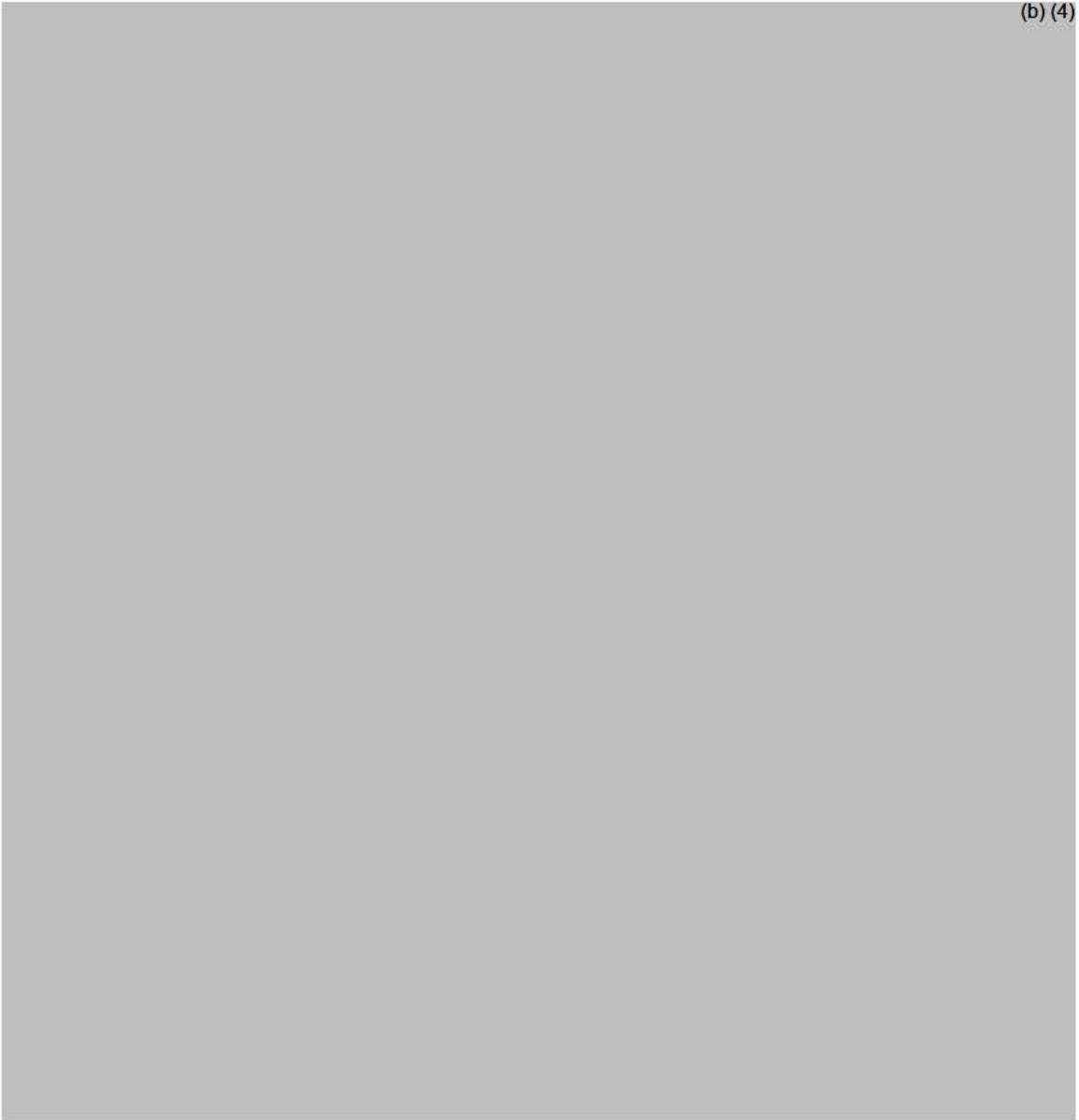
**Table 3. For Patients Weighing Less Than 45 kg: Volumes to add to IV Bag for 5 mcg/m<sup>2</sup>/day Dose**

(b) (4)

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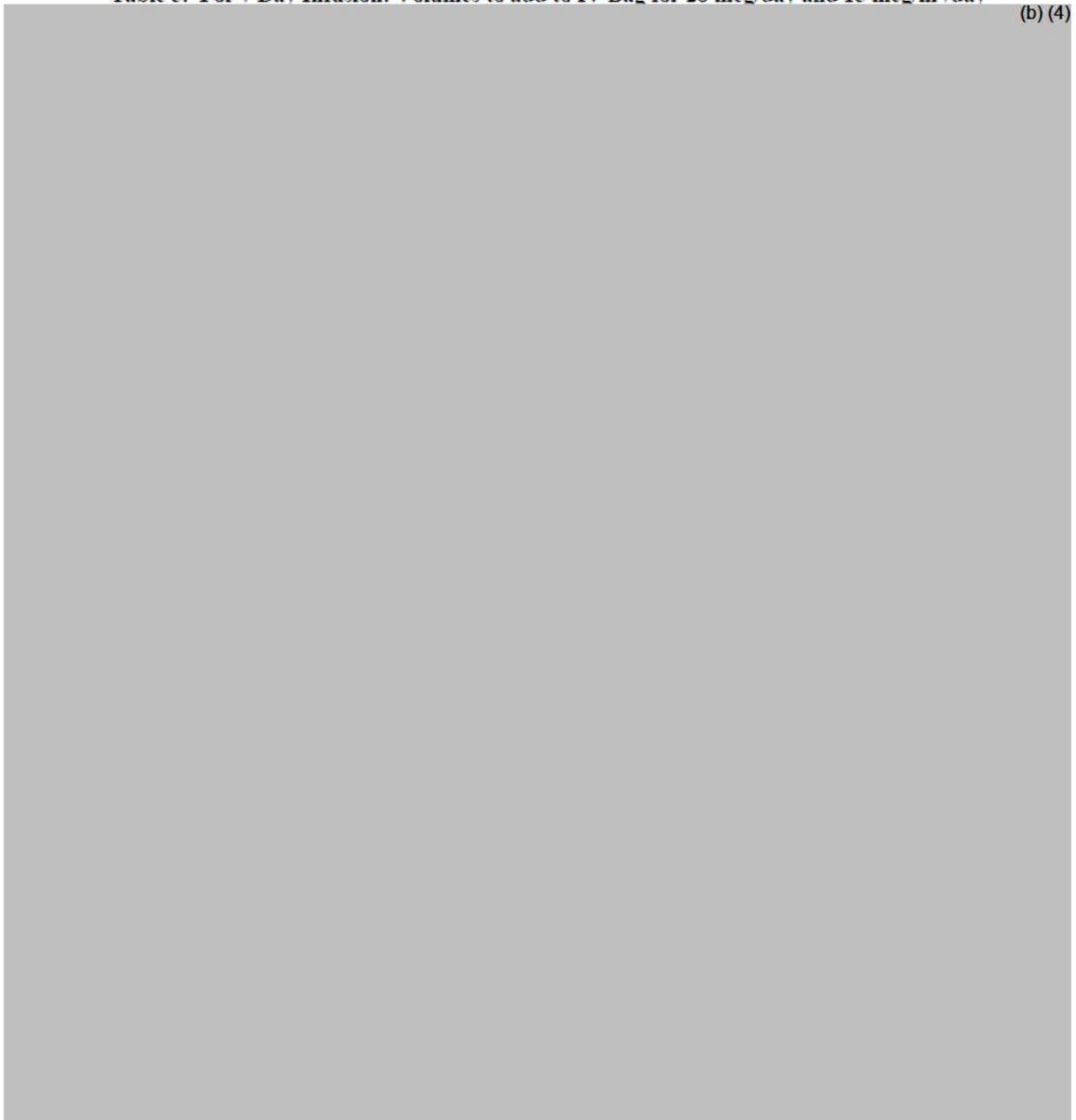
**Table 4. For Patients Weighing Less Than 45 kg: Volumes to add to IV Bag for 15 mcg/m<sup>2</sup>/day Dose**

(b) (4)



**Table 5. For 7 Day Infusion: Volumes to add to IV Bag for 28 mcg/day and 15 mcg/m<sup>2</sup>/day**

(b) (4)



C. Instructions for Admixture post summative study

**Table 2. For Patients Weighing Greater Than or Equal to 45 kg: Volumes to add to IV Bag**

<b>0.9% Sodium Chloride Injection, USP (starting volume)</b>			270 mL
<b>IV Solution Stabilizer</b>			5.5 mL
<b>Dose</b>	<b>Infusion Duration</b>	<b>Infusion Rate</b>	<b>Reconstituted BLINCYTO</b>
9 mcg/day	24 hours	10 mL/hour	0.83 mL
	48 hours	5 mL/hour	1.7 mL
28 mcg/day	24 hours	10 mL/hour	2.6 mL
	48 hours	5 mL/hour	5.2 mL*

\* 2 packages of BLINCYTO are needed for preparation of 28 mcg/day dose infused over 48 hours at a rate of 5 mL/hour<sup>2</sup>

**Table 3. For Patients Weighing Less Than 45 kg: Volumes to add to IV Bag for 5 mcg/m<sup>2</sup>/day Dose**

<b>0.9% Sodium Chloride Injection, USP (starting volume)</b>			270 mL	
<b>IV Solution Stabilizer</b>			5.5 mL	
<b>Dose</b>	<b>Infusion Duration</b>	<b>Infusion Rate</b>	<b>BSA (m<sup>2</sup>)</b>	<b>Reconstituted BLINCYTO</b>
<b>5 mcg/m<sup>2</sup>/day</b>	24 hours	10 mL/hour	1.5 – 1.59	0.7 mL
			1.4 – 1.49	0.66 mL
			1.3 – 1.39	0.61 mL
			1.2 – 1.29	0.56 mL
			1.1 – 1.19	0.52 mL
			1 – 1.09	0.47 mL
			0.9 – 0.99	0.43 mL
			0.8 – 0.89	0.38 mL
			0.7 – 0.79	0.33 mL
			0.6 – 0.69	0.29 mL
			0.5 – 0.59	0.24 mL
			0.4 – 0.49	0.2 mL
<b>5 mcg/m<sup>2</sup>/day</b>	48 hours	5 mL/hour	1.5 – 1.59	1.4 mL
			1.4 – 1.49	1.3 mL
			1.3 – 1.39	1.2 mL
			1.2 – 1.29	1.1 mL
			1.1 – 1.19	1 mL
			1 – 1.09	0.94 mL
			0.9 – 0.99	0.85 mL
			0.8 – 0.89	0.76 mL
			0.7 – 0.79	0.67 mL
			0.6 – 0.69	0.57 mL
			0.5 – 0.59	0.48 mL
			0.4 – 0.49	0.39 mL

**Table 4. For Patients Weighing Less Than 45 kg: Volumes to add to IV Bag for 15 mcg/m<sup>2</sup>/day Dose**

<b>0.9% Sodium Chloride Injection, USP (starting volume)</b>				270 mL
<b>IV Solution Stabilizer</b>				5.5 mL
<b>Dose</b>	<b>Infusion Duration</b>	<b>Infusion Rate</b>	<b>BSA (m<sup>2</sup>)</b>	<b>Reconstituted BLINCYTO</b>
<b>15 mcg/m<sup>2</sup>/day</b>	24 hours	10 mL/hour	1.5 – 1.59	2.1 mL
			1.4 – 1.49	2 mL
			1.3 – 1.39	1.8 mL
			1.2 – 1.29	1.7 mL
			1.1 – 1.19	1.6 mL
			1 – 1.09	1.4 mL
			0.9 – 0.99	1.3 mL
			0.8 – 0.89	1.1 mL
			0.7 – 0.79	1 mL
			0.6 – 0.69	0.86 mL
			0.5 – 0.59	0.72 mL
			0.4 – 0.49	0.59 mL
<b>15 mcg/m<sup>2</sup>/day</b>	48 hours	5 mL/hour	1.5 – 1.59	4.2 mL*
			1.4 – 1.49	3.9 mL*
			1.3 – 1.39	3.7 mL*
			1.2 – 1.29	3.4 mL*
			1.1 – 1.19	3.1 mL*
			1 – 1.09	2.8 mL
			0.9 – 0.99	2.6 mL
			0.8 – 0.89	2.3 mL
			0.7 – 0.79	2 mL
			0.6 – 0.69	1.7 mL
			0.5 – 0.59	1.4 mL
			0.4 – 0.49	1.2 mL

\*2 packages of BLINCYTO are needed for preparation of 15 mcg/m<sup>2</sup>/day dose infused over 48 hours at a rate of 5 mL/hour for patients with a BSA greater than 1.09 m<sup>2</sup>.

**Table 5. For 7 day Infusion: Volumes to add to IV Bag for 28 mcg/day and 15 mcg/m<sup>2</sup>/day**

<b>Bacteriostatic 0.9% Sodium Chloride (starting volume)</b>	90 mL
<b>IV Solution Stabilizer</b>	2.2 mL
<b>Reconstituted BLINCYTO</b>	Specific volume listed below in table
<b>Quantity Sufficient (qs) with 0.9% Sodium Chloride, USP to a Final Volume of 110 mL</b>	
<b>Infusion Duration</b>	7 days
<b>Infusion Rate</b>	0.6 mL/hour

Patient Weight	Dose	BSA (m <sup>2</sup> )	Number of BLINCYTO Packages	Reconstituted BLINCYTO	0.9% Sodium Chloride Injection, USP to qs to a Final Volume of 110 mL
Greater than or equal to 45 kg <i>(fixed-dose)</i>	28 mcg/day		6	16.8 mL	1 mL
(b) (4) <i>(BSA-based dose)</i>	15 mcg/m <sup>2</sup> /day	1.5 – 1.59	5	14 mL	3.8 mL
		1.4 – 1.49	5	13.1 mL	4.7 mL
		1.30 – 1.39	5	12.2 mL	5.6 mL
		1.20 – 1.29	5	11.3 mL	6.5 mL
		1.10 – 1.19	4	10.4 mL	7.4 mL
		1 – 1.09	4	9.5 mL	8.3 mL
		0.9 – 0.99	4	8.6 mL	9.2 mL
		(b) (4)			

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/s/  
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NICOLE B GARRISON  
03/14/2017

HINA S MEHTA  
03/14/2017

MISHALE P MISTRY  
03/14/2017

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125557Orig1s007**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## Kolibab, Kristopher

---

**From:** Kolibab, Kristopher  
**Sent:** Friday, April 28, 2017 12:07 AM  
**To:** Woo, Jennifer (jwoo01@amgen.com)  
**Subject:** BLA 125557 S-007/PI/Due April 28  
**Attachments:** BLA 125557 S7 PI April 28.docx

**Importance:** High

Hello Jennifer,

Please refer to BLA 125557 S-007 and the attached PI for your review. Please review the comment in the highlight section and provide a response.

Please officially submit the revised PI (in tracked changes and clean version word document) to the BLA and e-mail to me by **4 PM (EDT) Friday, April 28, 2017.**

**Please confirm receipt of this message by e-mail.**

Regards,

**Kris Kolibab, PhD**  
*Senior Regulatory Health Project Manager*  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration

Tel: 240-402-0277



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KRISTOPHER KOLIBAB  
04/28/2017

## Kolibab, Kristopher

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**From:** Kolibab, Kristopher  
**Sent:** Monday, April 24, 2017 5:36 PM  
**To:** Woo, Jennifer (jwoo01@amgen.com)  
**Subject:** BLA 125557 S-007/PI/Due May 1  
**Attachments:** BLA 125557 S7 PI April 24.docx

**Importance:** High

Hello Jennifer,

Please refer to BLA 125557 S-007 and the attached PI for your review.

Please review the changes/comments and do the following to the same draft:

- Please provide a response to the comments provided by the FDA
- **Accept any changes that you agree with including all format/minor editorial changes**
- Edit over the ones that you do not agree with (**do not reject any changes that the FDA proposed**)

After you have made the changes, please officially submit the revised PI (in tracked changes and clean version word document) to the BLA and e-mail to me by **9 AM (EDT) Monday, May 1, 2017**.

**Please confirm receipt of this message by e-mail.**

Regards,

**Kris Kolibab, PhD**  
*Senior Regulatory Health Project Manager*  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration

Tel: 240-402-0277



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KRISTOPHER KOLIBAB  
04/24/2017

## Kolibab, Kristopher

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**From:** Kolibab, Kristopher  
**Sent:** Wednesday, April 12, 2017 12:10 PM  
**To:** Woo, Jennifer (jwoo01@amgen.com)  
**Subject:** BLA 125557 S-007/PI and Med Guide/Due April 17  
**Attachments:** BLA 125557 S7 Med Guide April 12.doc; BLA 125557 S7 PI April 12.doc

**Importance:** High

Hello Jennifer,

Please refer to BLA 125557 S-007 and the attached PI and Medication Guide for your review.

Please review the changes/comments and do the following to the same draft:

- Please provide a response to the comments provided by the FDA
- **Accept any changes that you agree with including all format/minor editorial changes**
- Edit over the ones that you do not agree with (**do not reject any changes that the FDA proposed**)

After you have made the changes, please officially submit the revised PI (in tracked changes and clean version word document) and Medication Guide to the BLA and e-mail to me by **3 PM (EDT) Monday, April 17, 2017**.

**Please confirm receipt of this message by e-mail.**

Regards,

**Kris Kolibab, PhD**  
*Senior Regulatory Health Project Manager*  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration

Tel: 240-402-0277



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KRISTOPHER KOLIBAB  
04/12/2017

## Kolibab, Kristopher

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**From:** Kolibab, Kristopher  
**Sent:** Thursday, April 06, 2017 9:36 AM  
**To:** Woo, Jennifer (jwoo01@amgen.com)  
**Subject:** BLA 125557 S-007/Microbiology Information Request/Due April 18

**Importance:** High

Hello Jennifer,

Please refer to BLA 125557 S-007. Per the request of the microbiology review team please provide a response to the following information request by email to me and officially submit to the BLA by 10 AM(EDT) Tuesday April 18, 2017.

### **Microbiology Information Request:**

1. We note that each infusion solution was inoculated with approximately 100 CFUs/mL of each organism and that the CFUs/mL for each sample was determined by membrane filtration. However, the incubation conditions (media and temperature used) for each organism was not provided. Update section 3.2.P.2.5 with this information. Additionally, justify why a mold such as *Aspergillus brasiliensis* was not used in your study.

**Please confirm receipt of this message via e-mail.**

Regards,

**Kris Kolibab, PhD**  
*Senior Regulatory Health Project Manager*  
Center for Drug Evaluation and Research  
Office of Hematology and Oncology Products  
Division of Hematology Products  
U.S. Food and Drug Administration

Tel: 240-402-0277



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KRISTOPHER KOLIBAB  
04/06/2017

## Kolibab, Kristopher

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**From:** Kolibab, Kristopher  
**Sent:** Friday, March 10, 2017 1:21 PM  
**To:** Woo, Jennifer (jwoo01@amgen.com)  
**Subject:** BLA 125557 S-007/Labeling/Due March 17  
**Attachments:** BLA 125557 S-007 PI March 8.doc; BLA 125557 S-007 Med Guide.doc

**Importance:** High

Hello Jennifer,

Please refer to BLA 125557 S-007 and the attached PI and Medication Guide for your review.

Please review the changes/comments and do the following to the same draft:

- Please provide a response to the comments provided by the FDA
- **Accept any changes that you agree with including all format/minor editorial changes**
- Edit over the ones that you do not agree with (**do not reject any changes that the FDA proposed**)

After you have made the changes, please officially submit the revised PI (in tracked changes word document) and Medication Guide to the BLA and e-mail to me by **11 AM (EDT) Friday, March 17, 2017**.

**Please confirm receipt of this message by e-mail.**

Regards,

Kris Kolibab, PhD  
*Senior Regulatory Health Project Manager*  
*Division of Hematology Products*  
*OHOP/OND/CDER/FDA*

*Phone: 240-402-0277*

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KRISTOPHER KOLIBAB  
03/10/2017

## Kolibab, Kristopher

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**From:** Kolibab, Kristopher  
**Sent:** Tuesday, February 28, 2017 10:53 AM  
**To:** Woo, Jennifer (jwoo01@amgen.com)  
**Subject:** BLA 125557 S-007/Product Quality IR/Due March 14

**Importance:** High

Hello Jennifer,

Please refer to BLA 125557 S-007. Per the request of the product quality review team please provide a response to the following information request by email to me and officially submit to the BLA by **Tuesday 2pm (EST) March 14, 2017.**

### **Product Quality Information Request:**

1. No data to support the extractables-related safety of storage blinatumomab in infusion bags containing benzyl alcohol were included in the submission. Provide an evaluation of leachables, including a risk assessment, for dilution of blinatumomab in bacteriostatic saline with 0.74% benzyl alcohol at 25°C and 37°C and covering the 7 day planned administration. The evaluation should address the risk from potential leachables from polyolefin, PVC DEHP free, and ethyl vinyl acetate (EVA) infusion bags/pump cassettes and tubing sets. Analysis of leachables should include organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS), and metals (e.g., ICP-MS) species including their chemical identification and quantitation. Extractables data can be used to help inform the risk evaluation.

**Please confirm receipt of this message via e-mail.**

Regards,

**Kris Kolibab, PhD**  
**Senior Regulatory Health Project Manager**  
**Division of Hematology Products**  
**OHOP/OND/CDER/FDA**

**Phone: 240-402-0277**

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KRISTOPHER KOLIBAB  
02/28/2017



BLA 125557/S-007

**ACKNOWLEDGMENT --  
PRIOR APPROVAL SUPPLEMENT**

Amgen, Inc.  
Attention: Jennifer Woo, PhD  
Senior Manager, Regulatory Affairs  
One Amgen Center Drive  
Mail Stop 17-1-C  
Thousand Oaks, CA 91320-1799

Dear Dr. Woo:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

<b>BLA NUMBER:</b>	125557
<b>SUPPLEMENT NUMBER:</b>	S-007
<b>PRODUCT NAME:</b>	BLINCYTO (blinatumomab) lyophilized powder for solution (35 mcg), IV infusion
<b>DATE OF SUBMISSION:</b>	DECEMBER 1, 2016
<b>DATE OF RECEIPT:</b>	DECEMBER 1, 2016

This supplemental application proposes the following changes Blincyto: Updates to Prescribing Information (PI) and Medication Guide to incorporate new admixing instructions to prepare single, 7-day BLINCYTO infusion bags in conjunction with Bacteriostatic 0.9% Sodium Chloride, USP (containing 0.9% benzyl alcohol) as the preservative.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on JANUARY 30, 2017, in accordance with 21 CFR 601.2(a).

If the application is filed, the goal date will be June 1, 2017.

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

### **SUBMISSION REQUIREMENTS**

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Hematology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (240) 402-0277.

Sincerely,

*{See appended electronic signature page}*

Kris Kolibab, PhD  
Senior Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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KRISTOPHER KOLIBAB  
12/08/2016