

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125557Orig1s000**

**REMS**

**Initial Approval 12/2014**

**BLA 125557  
BLINCYTO™ (blinatumomab)**

**Drug Class: Bispecific CD19-directed CD3 T-cell engager**

Amgen Inc.  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799  
1-805-447-1000

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOAL(S):**

The goal of the BLINCYTO REMS is to mitigate the risk of cytokine release syndrome which may be life-threatening or fatal; the risk of neurological toxicities which may be severe, life-threatening, or fatal; and the risk of preparation and administration errors associated with use of BLINCYTO by:

- Informing healthcare providers about the risk of cytokine release syndrome which may be life-threatening or fatal
- Informing healthcare providers about the risk of neurological toxicities which may be severe, life-threatening, or fatal
- Informing pharmacists, who will prepare and dispense BLINCYTO, and nurses, who will administer BLINCYTO, about the risk of preparation and administration errors associated with use of BLINCYTO.

**II. REMS ELEMENTS**

**A. Communication Plan**

Amgen will implement the following communication plan for healthcare providers who are likely to prescribe or dispense BLINCYTO. The communication plan will consist of the following:

**1. REMS Letters**

Amgen will send a *REMS Letter for Healthcare Providers*, a *REMS Letter for Hospital and Home Healthcare Pharmacists*, and a *REMS Letter for Professional Societies* within 30 days of the REMS approval date and every 6 months for 18 months. The REMS Letters will address the risk of cytokine release syndrome which may be life-threatening or fatal; the risk of neurological toxicities which may be severe, life-threatening, or fatal; and the risk of preparation and administration errors associated with use of BLINCYTO. Email will be used as the primary method to disseminate the REMS Letters. If an email is marked as unopened, a second email will be sent

within 30 calendar days of the date the first email was sent. If the second email is marked as unopened, the REMS Letters will be mailed within 30 calendar days of the date the second email was sent. If a healthcare provider's or professional society's email address is not available or if the email is undeliverable, the REMS Letters will be mailed within 30 calendar days of the date of the bulk mailing. A link to the Prescribing Information (PI) and REMS Fact Sheet will accompany each REMS Letter.

- **REMS Letter for Healthcare Providers:** The intended audience for the *REMS Letter for Healthcare Providers* will be oncologists, oncology physician assistants, oncology nurse practitioners, hematologists, oncology nurses, home healthcare oncology nurses, and infusion nurses likely to administer BLINCYTO.
  - **REMS Letter for Hospital and Home Healthcare Pharmacists:** The intended audience for the *REMS Letter for Hospital and Home Healthcare Pharmacists* will be hospital-based pharmacists and home healthcare pharmacists.
  - **REMS Letter for Professional Societies:** Amgen will send the *REMS Letter for Professional Societies* to the following professional societies requesting the letter or content be provided to their membership:
    - American Society of Clinical Oncology (ASCO)
    - American Society of Hematology (ASH)
    - Oncology Nursing Society (ONS)
    - National Comprehensive Cancer Network (NCCN)
    - Hematology Oncology Pharmacy Association (HOPA)
    - American Pharmacists Association (APhA)
    - American Society of Health System Pharmacists (ASHP)
    - Home Health Nurses Association (HHA)
    - National Association for Home Care & Hospice (NAHCH)
    - Advanced Practitioner Society for Hematology and Oncology (APSHO)
2. **REMS Fact Sheet for Providers:** A *BLINCYTO REMS Fact Sheet for Providers* will be made available for healthcare providers and distributed by Amgen's sales representatives and medical field-based personnel during initial visits with healthcare providers for the first 12 months after the approval of the BLINCYTO REMS. Amgen's field based sales or medical representatives will discuss the risk messages contained in the Fact Sheet during the visit with the healthcare provider.
3. **Dissemination of REMS information at Scientific Meetings:** The BLINCYTO REMS materials will be prominently displayed at relevant scientific meetings where Amgen has a presence (e.g., exhibit booth) through 18 months following the REMS approval.

- 4. BLINCYTO REMS Website:** The BLINCYTO REMS website for healthcare providers ([www.blincytorems.com](http://www.blincytorems.com)) will continue for the duration of the REMS. The BLINCYTO REMS website will include the option to print the PI, Medication Guide, Important Safety Information, REMS Letter for Healthcare Providers, and the REMS Fact Sheet. The BLINCYTO website for healthcare providers will include a prominent REMS-specific link to the BLINCYTO REMS website.

The following are part of the BLINCYTO REMS and are appended:

- *REMS Letter for Healthcare Providers* (email and print versions)
- *REMS Letter for Hospital and Home Healthcare Pharmacists* (email and print versions)
- *REMS Letter for Professional Societies* (email and print versions)
- *BLINCYTO REMS Fact Sheet for Providers*
- BLINCYTO REMS Website (landing page)

### **III. Timetable for Submission of Assessments**

Amgen will submit REMS Assessments to the FDA at 18 months, 3 years, and 7 years from the date of approval of the initial REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Amgen will submit each assessment so that it will be received by the FDA on or before the due date.

**From:** Amgen Inc.

**To:** <Healthcare Provider email>

**Subject:** WARNING: Serious Risks Associated with BLINCYTO™



## BLINCYTO™ (blinatumomab) REMS

### FDA-REQUIRED REMS SAFETY INFORMATION

**Risk of:**

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal**
- **Neurological Toxicities, which may be severe, life threatening or fatal**
- **Preparation and Administration Errors**

December 2014

Dear Healthcare Provider:

The FDA has required this safety notice as part of the **BLINCYTO™ REMS (Risk Evaluation and Mitigation Strategy)** to inform you about the serious risks of BLINCYTO.

#### **BOXED WARNING: Cytokine Release Syndrome**

- 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.**
- The highest elevation of cytokines was observed in the first 2 days following start of BLINCYTO infusion.

#### **BOXED WARNING: Neurological Toxicities**

- In patients receiving BLINCYTO in clinical trials, neurological toxicities have occurred in approximately 50% of patients.
- The median time to onset of any neurological toxicity was 7 days.
- Grade 3 or higher (severe, life-threatening or fatal) neurological toxicities following initiation of BLINCYTO administration occurred in approximately 15% 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.

**Monitor patients closely for signs and symptoms of these events and interrupt or discontinue dosing of BLINCYTO.**

#### **OTHER SERIOUS RISKS: Preparation and Administration Errors**

- **It is very important that the instruction for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose).**

Please see the non-promotional REMS Fact Sheet, reviewed by the FDA available at [www.blincyto.rems.com](http://www.blincyto.rems.com) and the full Prescribing Information for more detailed safety information. Additional copies of the Fact Sheet and other important information are available at: [www.blincyto.rems.com](http://www.blincyto.rems.com).

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).

To review the Prescribing Information and Medication Guide, see links below:

[Prescribing Information](#)

[Medication Guide](#)

#### **REPORTING ADVERSE EVENTS**

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. Healthcare Providers should report all suspected adverse events associated with BLINCYTO to the FDA or to Amgen at 1-800-77-AMGEN (1-800-772-6436).

Sincerely,

Isma Benattia, MD, MBE  
Vice President, Global Patient Safety

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Vice President, Global Patient Safety

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**From:** Amgen Inc.

**To:** <Pharmacist Email>

**Subject:** WARNING: Serious Risks Associated with BLINCYTO™



## BLINCYTO™ (blinatumomab) REMS

### FDA-REQUIRED REMS SAFETY INFORMATION

**Risk of:**

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal**
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December 2014

Dear Pharmacist:

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**Monitor patients closely for signs and symptoms of these events and interrupt or discontinue dosing of BLINCYTO.**

#### **OTHER SERIOUS RISKS: Preparation and Administration Errors**

- **It is very important that the instruction for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose).**

## Special Considerations to Support Accurate Preparation

- IV Solution Stabilizer is provided and is used to coat the prefilled IV bag prior to addition of reconstituted BLINCYTO.
- Reconstitute BLINCYTO with Sterile Water for Injection, USP, only.
- Aseptic technique must be done in a USP <797> compliant facility and strictly observed when preparing the solution for infusion since BLINCYTO does not contain antimicrobial preservatives.
- Use the specific volumes described in the admixing instructions.
- **Please see the full Prescribing Information for important details on preparation and administration, including storage requirements for BLINCYTO.**

Please see the non-promotional REMS Fact Sheet, reviewed by the FDA available at [www.blincyto.rems.com](http://www.blincyto.rems.com) and the full Prescribing Information for more detailed safety information. Additional copies of the Fact Sheet and other important information are available at: [www.blincyto.rems.com](http://www.blincyto.rems.com).

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To review the Prescribing Information and Medication Guide, see links below:

[Prescribing Information](#)

[Medication Guide](#)

## REPORTING ADVERSE EVENTS

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Sincerely,

Isma Benattia, MD, MBE  
Vice President, Global Patient Safety

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## BLINCYTO<sup>™</sup> (blinatumomab) REMS

### FDA-REQUIRED REMS SAFETY INFORMATION

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December 2014

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**From:** Amgen Inc.

**To:** <Professional Society email>

**Subject:** WARNING: Serious Risks Associated with BLINCYTO™



## BLINCYTO™ (blinatumomab) REMS

### FDA-REQUIRED REMS SAFETY INFORMATION

**Risk of:**

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December 2014

### IMPORTANT SAFETY NOTICE

Dear <name>:

The FDA has required this safety notice as part of the **BLINCYTO™ REMS (Risk Evaluation and Mitigation Strategy)** to be distributed to the <insert Professional Society Name>. Amgen requests that you distribute the information to your members, informing them about the serious risks of BLINCYTO.

#### **BOXED WARNING: Cytokine Release Syndrome**

- 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.**
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**Monitor patients closely for signs and symptoms of these events and interrupt or discontinue dosing of BLINCYTO.**

## **OTHER SERIOUS RISKS: Preparation and Administration Errors**

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- The highest elevation of cytokines was observed in the first 2 days following start of BLINCYTO infusion.

#### **BOXED WARNING: Neurological Toxicities**

- In patients receiving BLINCYTO in clinical trials, neurological toxicities have occurred in approximately 50% of patients.
- The median time to onset of any neurological toxicity was 7 days.
- Grade 3 or higher (severe, life-threatening or fatal) neurological toxicities following initiation of BLINCYTO administration occurred in approximately 15% 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.

**Monitor patients closely for signs and symptoms of these events and interrupt or discontinue dosing of BLINCYTO.**

# BLINCYTO™ (blinatumomab) REMS

## OTHER SERIOUS RISKS: Preparation and Administration Errors

- **It is very important that the instruction for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose).**

Please see the enclosed non-promotional REMS Fact Sheet, reviewed by the FDA and the full Prescribing Information for more detailed safety information. Additional copies of the Fact Sheet, and other important information are available at: [www.blincyto.rems.com](http://www.blincyto.rems.com).

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## BLINCYTO<sup>™</sup> REMS FACT SHEET FOR HEALTHCARE PROVIDERS

### FDA-REQUIRED REMS SAFETY INFORMATION

**Risk of:**

- **Cytokine Release Syndrome (CRS), which may be life-threatening or fatal**
- **Neurological toxicities, which may be severe, life threatening or fatal**
- **Preparation and Administration Errors**

### **BOXED WARNING**

#### **Cytokine Release Syndrome**

- Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO<sup>™</sup>.
- 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.
- 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.
- The highest elevation of cytokines was observed in the first 2 days following start of BLINCYTO infusion.

#### **Neurological Toxicities**

- In patients receiving BLINCYTO in clinical trials, neurological toxicities have occurred in approximately 50% of patients.
- The median time to onset of any neurological toxicity was 7 days.
- Grade 3 or higher (severe, life-threatening or fatal) neurological toxicities following initiation of BLINCYTO administration occurred in approximately 15% 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.

**Monitor patients closely for signs or symptoms of these events and interrupt or discontinue BLINCYTO dosing.**

## OTHER SERIOUS RISKS:

### Preparation and Administration Errors

- Preparation and administration errors have occurred with BLINCYTO treatment.
- **It is very important that the instructions for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose).**
- Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.
- See Dosage and Administration section of Prescribing Information for detailed safety information.

### MORE INFORMATION

For detailed information regarding BLINCYTO including storage, preparation, and administration, it is essential that you read the Prescribing Information for BLINCYTO.

### INDICATION

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).

### WHAT IS THE BLINCYTO™ REMS?

A REMS (**R**isk **E**valuation and **M**itigation **S**trategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. The FDA has determined that a REMS is necessary to ensure that the benefits of BLINCYTO outweigh its risks. The purpose of the BLINCYTO REMS is to inform Healthcare Providers of the risks of serious neurological toxicities, cytokine release syndrome, and preparation and administration errors. This Fact Sheet is required by the FDA as part of the BLINCYTO REMS program.

Please visit [www.blincyto.rems.com](http://www.blincyto.rems.com) for further information and resources.

This fact sheet does not contain the complete safety profile for BLINCYTO. Please refer to the full Prescribing Information, including **BOXED WARNINGS** and Medication Guide.

### REPORTING ADVERSE EVENTS

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. Healthcare Providers should report all suspected adverse events associated with BLINCYTO to the FDA or to Amgen at 1-800-77-AMGEN (1-800-772-6436).



## BLINCYTO™ (blinatumomab) Risk Evaluation and Mitigation Strategy (REMS)

### What is the BLINCYTO™ REMS?

A Risk Evaluation and Mitigation Strategy (REMS) is a program to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

The purpose of the BLINCYTO REMS is to inform Healthcare Providers about the following serious risks:

#### **BOXED WARNING: Cytokine Release Syndrome**

- 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.**
- The highest elevation of cytokines was observed in the first 2 days following start of BLINCYTO infusion

#### **BOXED WARNING: Neurological Toxicities**

- In patients receiving BLINCYTO in clinical trials, neurological toxicities have

### Materials for Healthcare Providers

#### BLINCYTO™ REMS Letter for Healthcare Providers

➤ [Download PDF](#) 

#### BLINCYTO™ REMS Letter for Hospital and Home Healthcare Pharmacists

➤ [Download PDF](#) 

#### BLINCYTO™ REMS Fact Sheet for Healthcare Providers

➤ [Download PDF](#) 

occurred in approximately 50% of patients.

- The median time to onset of any neurological toxicity was 7 days.
- Grade 3 or higher (severe, life-threatening or fatal) neurological toxicities following initiation of BLINCYTO administration occurred in approximately 15% 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.

### Preparation and Administration Errors

- Preparation and administration errors have occurred with BLINCYTO treatment.
- **It is very important that the instructions for preparation (including admixing) and administration are strictly followed to minimize medication errors (including underdose and overdose).**

### BLINCYTO Fact Sheet:

A non-promotional REMS Fact Sheet reviewed by the FDA, with more detailed information on the serious risks associated with BLINCYTO is available in the “Materials for Healthcare Providers” section above.

### INDICATION:

**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).

You are encouraged to report negative side effects of **BLINCYTO** to Amgen at 1-800-77-AMGEN (1-800-772-6436) and/or the FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088

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