

Initial REMS approval: 12/2014

Most recent modification: 08/2016

**BLA 125557
BLINCYTO® (blinatumomab)
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 goals of the BLINCYTO REMS are 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 must implement the following communication plan to healthcare providers likely to prescribe and pharmacists likely to dispense BLINCYTO. The communication plan must include:

1. REMS Letters

- Amgen must send a *REMS Letter for Healthcare Providers*, a *REMS Letter for Hospital and Home Healthcare Pharmacists*, and a *REMS Letter for Professional Societies* within 60 calendar days from the date of approval of this REMS modification (August 2016). Amgen must send a second emailing 12 months from the date of approval of this REMS modification. The REMS Letters must 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 must be the

primary method to disseminate the REMS Letters. If an email is marked as unopened, a second email must 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 must be mailed within 30 calendar days of the date the second email was sent. If a healthcare provider's, pharmacist's or professional society's email address is not available or if the email is undeliverable, the REMS Letters must be mailed within 30 calendar days of the date the first sets of emails were sent. A copy of or link to the Prescribing Information (PI) and *REMS Fact Sheet* must accompany each REMS Letter. Amgen must make the *REMS Letter for Healthcare Providers* and *REMS Letter for Hospital and Home Healthcare Pharmacists* available via a link from the *BLINCYTO REMS Program Website* and through Amgen field based sales and medical representatives upon request for 12 months after the approval of this REMS modification.

- **REMS Letter for Healthcare Providers:** The intended audience for the *REMS Letter for Healthcare Providers* must be oncologists, oncology physician assistants, oncology nurse practitioners, hematologists, oncology nurses, home healthcare oncology nurses, and infusion nurses. This includes healthcare providers who have prescribed BLINCYTO within the previous 12 months from the approval of this REMS modification and healthcare providers likely to prescribe or administer BLINCYTO.
- **REMS Letter for Hospital and Home Healthcare Pharmacists:** The intended audience for the *REMS Letter for Hospital and Home Healthcare Pharmacists* must be hospital-based pharmacists and home healthcare pharmacists.
- **REMS Letter for Professional Societies:** The intended audience for the *REMS Letter for Professional Societies* must be the following professional societies and organizations. Amgen must request the letter or content be provided to the societies' members:
 - 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)
 - American Society of Pediatric Hematology/Oncology (ASPHO)
 - Association of Pediatric Hematology/Oncology Nurses (ASPHON)

2. **REMS Fact Sheet:** A *BLINCYTO REMS Fact Sheet for Providers* must be made available for healthcare providers and disseminated through Amgen's field based sales or medical representatives during the initial or follow-up discussion with healthcare providers within the first 12 months after the approval of this REMS modification (August 2016). Amgen's field based sales or medical representatives must orally review the risk messages contained in the *BLINCYTO REMS Fact Sheet for Providers* during the visit with the healthcare provider.
3. **Dissemination of REMS information at Scientific Meetings:** The BLINCYTO REMS materials must be prominently displayed and disseminated together with responses to medical information requests at all relevant scientific meetings where Amgen has a presence (e.g., exhibit booth) for 12 months following the approval of this REMS modification (August 2016).
4. **REMS Program Website:** The *BLINCYTO REMS Program Website* (www.blincytoREMS.com) must continue for 3 years from the date of initial approval of the REMS (12/03/2014). The *BLINCYTO REMS Program Website* must include the option to print the currently approved PI, Medication Guide, *REMS Letter for Healthcare Providers*, *REMS Letter for Hospital and Home Healthcare Pharmacists*, and *REMS Factsheet*. The BLINCYTO product website must include a prominent REMS-specific link to the *BLINCYTO REMS Program Website*. All website information must be updated within 60 calendar days from the date of approval of this REMS modification (August 2016).

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 Program Website*

III. Timetable for Submission of Assessments

Amgen must submit REMS Assessments to the FDA at 18 months, 3 years, and 7 years from the date of the initial approval of the REMS (12/03/2014). 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 calendar days before the submission date for that assessment. Amgen must submit each assessment so that it will be received by the FDA on or before the due date.

BLINCYTO[®] 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[®].
- 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.
- Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.

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.
- 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.

Monitor patients closely for signs and symptoms of these events and interrupt or discontinue

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).
- Please note that the recommended dose for BLINCYTO is 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).
- 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.blincytolems.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 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).

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**

August 2016

Dear Healthcare Provider:

The FDA has required this safety notice as part of the **BLINCYTO® REMS** (**R**isk **E**valuation and **M**itigation **S**trategy) 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.
- Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.

BOXED WARNING: 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.
- 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.

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 note that the recommended dose for BLINCYTO is 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).

Please see the non-promotional REMS Fact Sheet, reviewed by the FDA available at 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.

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

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Sincerely,

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

BLINCYTO® is a trademark of Amgen Inc.
©2016 Amgen Inc. All rights reserved.



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**
- **Neurological Toxicities, which may be severe, life-threatening or fatal**
- **Preparation and Administration Errors**

August 2016

Dear Pharmacist:

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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.
- Hospitalization is recommended for the first 9 days of the first cycle and the first 2 days of the second cycle.

BOXED WARNING: 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.
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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).**
- Please note that the recommended dose for BLINCYTO is 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).

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 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.

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

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Sincerely,

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

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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

August 2016

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

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BLINCYTO[®] (blinatumomab) REMS

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August 2016

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- 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 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.

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).

REPORTING ADVERSE EVENTS

You are encouraged to report negative side effects of prescription drugs to the FDA.

Visit 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

From: Amgen Inc.
To: <Professional Society 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**

August 2016

IMPORTANT SAFETY NOTICE

Dear [name]:

The FDA has required this safety notice as part of the **BLINCYTO® REMS** (**R**isk **E**valuation and **M**itigation **S**trategy) 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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August 2016

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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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).

Sincerely,

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



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

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Preparation and Administration Errors

- Preparation and administration errors have occurred with BLINCYTO treatment.
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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 or call 1-800-FDA-1088

Materials for Healthcare Providers

BLINCYTO® REMS Letter for Healthcare Providers

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BLINCYTO® REMS Letter for Hospital and Home Healthcare Pharmacists

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August 2016

IMPORTANT DRUG WARNING

Subject: New Safety Information for BLINCYTO (blinatumomab) - Risk of Pancreatitis

Dear Health Care Provider:

The purpose of this letter is to inform you of important safety information for BLINCYTO, a bispecific CD19-directed CD3 T-cell engager approved 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.

Risk of Pancreatitis with use of BLINCYTO

- As of February 2016, events of pancreatitis, some life-threatening or fatal, have been reported in 10 patients out of approximately 2000 patients from clinical trials and the post-marketing setting. High-dose steroid therapy may have contributed, in some cases, to the pancreatitis.
- Although in some cases there were confounding medications and occasionally missing information, the association of pancreatitis with BLINCYTO administration, the frequency and seriousness of events, and a positive dechallenge/positive rechallenge case warrant an update to the BLINCYTO prescribing information.

Prescriber Action

- Evaluate patients who develop signs and symptoms of pancreatitis.
- Management of pancreatitis may require either temporary interruption or discontinuation of BLINCYTO.

Action being taken by Amgen

Amgen has worked with the FDA to include language regarding pancreatitis in Section 5 Warnings and Precautions and Section 6 Adverse Reactions of the BLINCYTO prescribing information. The medication guide has also been updated to include this new information.

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

Further information on the safety concern

In clinical trials, 6 cases suggestive of pancreatitis were reported in patients receiving BLINCYTO. Two cases described increase in pancreatic enzymes (such as increased lipase) with associated symptoms. Four cases (3 non-serious and 1 serious) reported adverse events of pancreatitis. The 1 serious event of pancreatitis was reported in a patient with elevations of lipase and total bilirubin before treatment with BLINCYTO; the event did not resolve with the discontinuation of BLINCYTO.

In the post-marketing setting, 4 cases reported events of pancreatitis (n=2), acute pancreatitis (n=1), and necrotizing pancreatitis (n=1). The case of necrotizing pancreatitis, with a fatal outcome, was reported in

a patient receiving dexamethasone and prior treatment with multiple chemotherapy regimens. In this patient, increase in lipase levels coincided with the dexamethasone dosing during the administration of BLINCYTO; the patient's course was complicated by colitis and sepsis. In one of the cases that reported an event of pancreatitis, the symptoms subsided upon temporary withdrawal of BLINCYTO and recurred after resuming treatment (positive dechallenge/positive rechallenge). The remaining post-marketing cases described 1 patient with an event of pancreatitis in the context of leukemic infiltration; and 1 patient with an event of acute pancreatitis in the setting of concurrent appendicitis.

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, 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

Enclosure(s): BLINCYTO Full Prescribing Information, Medication Guide

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
08/30/2016