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C.R. 1010332727- C.C.No.275329

January 2017

The Saudi Food and Drug Authority has required this safety notice as part of the BLINCYTO® (Blinatumomab) RMP (Risk Management Plan) to inform you about the serious risks of BLINCYTO.

Dear Healthcare Professional,

Amgen would like to inform you of the following serious risks: Preparation and Administration Errors, Pancreatitis, Cytokine Release Syndrome (CRS) and Neurological Toxicities of BLINCYTO

Summary:

Preparation and Administration Errors

- BLINCYTO is administered by continuous intravenous infusion at 9 mcg/day for the first 7 days of treatment and then increased to 28 mcg/day for the remaining days of the first cycle and for subsequent cycles (see section 4.2 of the prescribing information)
- Prior to administration, confirm the correct infusion rate (see section 6.6 of the prescribing information)

Risk of Pancreatitis

- As of February 2016, events of pancreatitis, some life-threatening or fatal, have been reported in 10 patients, out of approximately 2000 patients, who have been exposed to Blincyto in the clinical trial and post-marketing settings. High-dose steroid therapy may have contributed, in some cases, to the pancreatitis.
- Evaluate patients who develop signs and symptoms of pancreatitis.
- Management of pancreatitis may require either temporary interruption or discontinuation of Blincyto.

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

Neurological Toxicities

- Physicians should counsel patients regarding the safe and effective use of the drug and ensure they are aware of the important selected risks outlined in this letter.

- Physicians should monitor patients closely for signs and symptoms of these events and interrupt or discontinue dosing of BLINCYTO.

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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).

The following medication errors have been observed during preparation and administration (including overdose) of BLINCYTO:

- Pharmacy preparation errors due to miscalculation of BLINCYTO concentration
- Increased infusion flow rates due to manipulation of the pump by the patient, infusion rate set incorrectly, and IV line connected to the pump incorrectly
- Using incorrect diluent to reconstitute BLINCYTO lyophilized powder
- Priming of the IV line with the incorrect solution
- Failure to follow aseptic technique during preparation as BLINCYTO does not contain antimicrobial preservatives

Summary of Recommendations for Health Care Professionals

- BLINCYTO is administered by continuous intravenous infusion at 9 mcg/day for the first 7 days of treatment and then increased to 28 mcg/day for the remaining days of the first cycle and for subsequent cycles (see section 4.2 of the prescribing information)
- Prior to administration, confirm the correct infusion rate (see section 6.6 of the prescribing information)

Special considerations to help ensure accurate preparation and administration include:

- **Use aseptic technique**
  - Performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.
  - Prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.

- **Follow prescribed dosing and specified admixing volumes**

  o Verify the prescribed BLINCYTO dose before beginning preparation

  o Use the specific volumes described in the admixing instructions to minimize errors in calculation. The specific volumes account for the overfill in the prefilled Sodium Chloride IV bags and ensure that the patient will receive the full dose of BLINCYTO. Do not recalculate the volumes

- **Prepare the IV bag for the BLINCYTO solution**
  o **Reconstitute with preservative-free Sterile Water for Injection**
  o IV Solution Stabilizer is provided with the BLINCYTO package and is used to coat the prefilled IV bag prior to addition of reconstituted BLINCYTO to prevent adhesion of BLINCYTO to IV bags and IV lines; do not use IV solution stabilizer for reconstitution of BLINCYTO

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- **Prime the IV line**
  - Use only the prepared BLINCYTO solution for infusion to prime the IV line
  - Use IV tubing that contains an in-line, sterile, non-pyrogenic, low protein-binding 0.2-micron filter

- **Use of infusion pump**
  - The infusion pump should be programmable, lockable, and non-elastomeric, with an alarm
  - BLINCYTO should be infused through a dedicated lumen
  - Do not flush the infusion lines into the patient, as it will cause an inadvertent bolus of drug to be administered
  - Advise patients not to adjust the settings on the infusion pump ○ Advise patients to contact their health care professional in case of pump malfunction

- The IV bag must only be changed by a health care professional

- Ensure that other health care professionals within your team who are involved in providing care to patients treated with BLINCYTO are informed of this important safety information regarding medication errors.

New Safety Information: Risk of Pancreatitis

Summary of the issue

Summary:

Amgen would like to inform you of the following:

As of February 2016, events of pancreatitis, some life-threatening or fatal, have been reported in 10 patients, out of approximately 2000 patients, who have been exposed to Blincyto in the clinical trial and post-marketing settings. High-dose steroid therapy may have contributed, in some cases, to the pancreatitis.

Further information on the safety concern and the recommendations

In clinical trials, 6 cases suggestive of pancreatitis were reported in patients receiving Blincyto. Two cases described increases 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, increases in lipase levels coincided with the dexamethasone dosing during the administration of Blincyto; the patient's course was

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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.
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.

Action being taken by Amgen

Amgen is working with SFDA to include language regarding pancreatitis in the Warnings and Precautions and Adverse Reactions sections of the Blincyto prescribing information. The patient information leaflet will be updated to include this new information.

Summary of Recommendations for Health Care Professionals

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

Cytokine Release Syndrome (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.**
- 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.

Summary of Recommendations for Health Care Professionals

Physicians should counsel patients regarding the safe and effective use of the drug and ensure they are aware of the important selected risks outlined in this letter.

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Physicians should monitor patients closely for signs and symptoms of these events and interrupt or discontinue dosing of BLINCYTO.

Further Information

For detailed information regarding BLINCYTO including storage, preparation, and administration, it is essential that you read the prescribing information for BLINCYTO enclosed with this letter.

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 letter is being sent with the agreement of Saudi Food and Drug Authority (SFDA).

Call for reporting

Any suspected adverse reactions should be reported immediately to local Amgen representative or the National Pharmacovigilance and Drug Safety Center

Amgen Local Representative in Saudi Arabia is Salehiya Trading Est,

Tel #: +966 1 1464 6955 Ext 763 Or
E-mail: s.almardi@salehiya.com
The National Pharmacovigilance & Drug safety Centre (NPC)

Saudi Food and Drug Authority (SFDA)
Fax: +966-11-2057662
Email: npc.drug@sfda.gov.sa Online: http://ade.sfda.gov.sa/

Should you have any questions or require additional information regarding the use of Blincyto, please contact Amgen Medical Information on 00971 4 4396800 or by e-mail at: meamedinfo@amgen.com

Sincerely,

Nasser Alrajhi
Regulatory Affairs Senior Manager
Amgen Saudi Arabia

Yasser Al Ahmary
Senior Associate Global Safety
Amgen Saudi Arabia

Sibel Barti
Medical Director
GCC,Egypt Cluster

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