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C.R 1010332727 C.C.NO. 275329

Direct Health Care Professional Communication

Date: May 2019

Dear Health Care Professional,

Subject: BLINCYTO (blinatumomab) - Important Information: Special Considerations to Minimize Occurrence of Medication Errors and Benzyl alcohol toxicity warning for 7-day infusion solution due to the addition of bacteriostatic saline, for pediatric patients, particularly neonates and premature infants.

Medication Errors:

Amgen would like to inform you of the need to strictly follow the preparation and administration instructions for BLINCYTO outlined in the prescribing information, in order to reduce the risk of medication errors.

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
- The choice of BLINCYTO dose is based on body weight
- Prior to administration, confirm the correct infusion rate

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Treatment of Relapsed or Refractory B-cell precursor ALL

- **In patients greater than or equal to 45 kg,** BLINCYTO is administered 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
- **In patients less than 45 kg,** the dose is calculated using the patient's body surface area (BSA). In these patients, BLINCYTO is administered at 5 mcg/m2/day for the first 7 days of treatment and then increased to 15 mcg/m2/day for the remaining days of the first cycle and for subsequent Cycles

Treatment of MRD-positive B-cell Precursor ALL

- **In patients greater than or equal to 45 kg,** BLINCYTO is administered at 28 mcg/day for all treatment cycles
- **In patients less than or equal to 45 kg,** BLINCYTO is administered at 15 mcg/m^2/day for all treatment cycles

Special considerations to help ensure accurate preparation and administration include:

- Use aseptic technique
  - Aseptic technique must be strictly observed when preparing the solution for infusion since BLINCYTO vials does not contain antimicrobial preservatives
  - Preparation must be done in a USP <797>/EU GMP compliant facility
  - Preparation must be done in an ISO Class 5 laminar flow hood or better
- Follow prescribed dosing and specified admixing volumes
  - Verify the prescribed BLINCYTO dose before beginning preparation
  - 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.

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- Prepare the IV bag for the BLINCYTO solution
  - Reconstitute with preservative-free Sterile Water for Injection
  - 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 tubing; do not use IV solution stabilizer for reconstitution of BLINCYTO

- Prime the IV line
  - Use only the prepared BLINCYTO solution for infusion to prime the IV tubing
  - 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.

Benzyl alcohol toxicity warning for 7-day infusion:

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.

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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).

Summary of the issue

Blincyto has recently been approved allowing the option of preparing a 7-day bag for continuous infusion, containing Bacteriostatic 0.9% Sodium Chloride (containing 0.9% benzyl alcohol) as the preservative. This option is available for patients weighing ≥ 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.

Action being taken by Amgen

Amgen is working with SFDA to include language regarding benzyl alcohol toxicity in the **Special Warnings and Precautions for Use** and **Special Populations** 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

Prepare preservative-free Blincyto solution for infusion (24 hour, 48 hour, 72 hour, or 96 hour bags) for use in neonates, infants, and patients weighing < 22 kg; 7-day infusion bag containing bacteriostatic saline is not recommended for use in these patients.

Further Information

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 bags of Blincyto solution for infusion contain benzyl alcohol. The minimum amount of benzyl alcohol at which toxicity may occur is not known. The "gasping 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

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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.

The information in this letter has been approved by the Saudi Food and Drug Authority (SFDA).

Contact details for adverse event reporting or to request further information
Any suspected adverse reactions should be reported immediately to local Amgen QPPV or the National Pharmacovigilance and Drug Safety Center

Amgen Local QPPV in Saudi Arabia is Yasser Al-Ahmary,

Tel #: +966 112 799328
E-mail: ymohamma@amgen.com

The National Pharmacovigilance & Drug safety Centre (NPC)

Saudi Food and Drug Authority (SFDA)
SFDA call center 19999
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Fax: +966-11-2057662
E-mail: 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 Medical Information on +966 11 2799394 or by e-mail at: meamedinfo@amgen.com

Sincerely,

Nasser Alrajhi
Regulatory Affairs Head
Amgen GCC

Yasser Al-Ahmary
Senior Associate Global Safety
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Dr. Sameh Rakha
Medical Director
Amgen GCC

Sameh Rakha