Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	October 24, 2023
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Product Name:	Blincyto (blinatumomab)
Pediatric Labeling Approval Date:	August 30, 2016
Application Type/Number:	BLA 125557
Applicant:	Amgen
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Blincyto (blinatumomab) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with blinatumomab in pediatric patients.

Blincyto (blinatumomab) is a bispecific CD19-directed CD3 T-cell engager and was initially approved in the U.S. on December 3, 2014. Blinatumomab is currently indicated for the treatment of adult and pediatric patients with:

- CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.
- Relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia.

This pediatric postmarketing safety review was stimulated by the pediatric labeling on August 30, 2016, which established the safety and efficacy of blinatumomab in patients weighing < 45 kg with Philadelphia chromosome negative relapsed or refractory B-cell precursor ALL.

DPV reviewed all U.S. serious FAERS reports with blinatumomab in pediatric patients less than 18 years of age from December 3, 2014, to June 13, 2023. Of the 205 reports reviewed, one case was included in our case series. We identified a singular case reporting the unlabeled event of akathisia. The case was possibly related to blinatumomab; however, additional evaluation of the FAERS database and medical literature did not identify sufficient evidence to support a signal of akathisia with blinatumomab at this time.

Overall, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with blinatumomab in pediatric patients less than 18 years of age.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Blincyto (blinatumomab) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with blinatumomab in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Blincyto (blinatumomab) is a bispecific CD19-directed CD3 T-cell engager and was initially approved in the U.S. on December 3, 2014. Blinatumomab is currently indicated for the treatment of adult and pediatric patients with:[1]

- CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%.
- Relapsed or refractory CD19-positive B-cell precursor acute lymphoblastic leukemia.

This pediatric postmarketing safety review was stimulated by the pediatric labeling on August 30, 2016, which established safety and efficacy of blinatumomab in patients weighing < 45 kg with Philadelphia chromosome negative relapsed or refractory B-cell precursor ALL.[2]

A pediatric safety review for blinatumomab has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The blinatumomab labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional blinatumomab labeling information, please refer to the full prescribing information.[1]

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 and treat with corticosteroids 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)**

----------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)
- Benzyl Alcohol Toxicity in Neonates: Use BLINCYTO prepared with preservative-free saline for neonates. (5.12, 8.4)
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.13, 8.1, 8.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥ 20%) are pyrexia, infusion-related reactions, infections (pathogen unspecified), headache, neutropenia, anemia, and thrombocytopenia. (6.1)

8.4 Pediatric Use

Minimal Residual Disease (MRD)-Positive B-cell Precursor ALL

The safety and efficacy of BLINCYTO for the treatment of CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% have been established in pediatric patients. Use of BLINCYTO is supported by evidence from two randomized, controlled trials (Study AALL1331 NCT02101853 and Study 20120215 NCT02393859) in pediatric subjects with first relapsed B-cell precursor ALL. Both studies included pediatric patients with MRD-positive B-cell precursor ALL. The studies included pediatric patients treated with BLINCYTO in the following age groups: 6 infants (1 month up to less than 2 years), 165 children (2 years up to less than 12 years), and 70 adolescents (12 years to less than 17 years). In general, the adverse reactions in BLINCYTO-treated pediatric patients were similar in type to those seen in adult patients with MRD-positive ALL *[see Adverse Reactions (6.1)]*, and no differences in safety were observed between the different pediatric age subgroups.

Relapsed or Refractory B-cell Precursor ALL

The safety and efficacy of BLINCYTO have been established in pediatric patients with relapsed or refractory B-cell precursor ALL. 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 *[see Clinical Studies (14.2)]*.

In general, the adverse reactions in BLINCYTO-treated pediatric patients with relapsed or refractory ALL were similar in type to those seen in adult patients with relapsed or refractory B-cell precursor ALL *[see Adverse Reactions (6.1)]*. Adverse reactions that were observed more frequently (≥ 10% difference) in the pediatric population compared to the adult population were pyrexia (80% vs. 61%), hypertension (26% vs. 8%), anemia (41% vs. 24%), infusion-related reaction (49% vs. 34%), thrombocytopenia (34% vs. 21%), leukopenia (24% vs. 11%), and weight increased (17% vs. 6%).

In pediatric patients less than 2 years old (infants) with relapsed or refractory ALL, 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 (17%).

Benzyl Alcohol Toxicity in Neonates

Serious and fatal adverse reactions, including "gasping syndrome," can occur in very low birth weight (VLBW) neonates born weighing less than 1500 g, and early preterm neonates (infants born less than 34 weeks gestational age) treated with benzyl alcohol-preserved drugs intravenously. The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. In these cases, benzyl alcohol dosages of 99 to 234 mg/kg/day produced high concentrations of benzyl alcohol and its metabolite in the blood and urine (blood concentration 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. The minimum amount of benzyl alcohol at which serious adverse reactions may occur in neonates is not known *[see Warnings and Precautions (5.12)]*.

Use the preservative-free formulations of Blincyto where possible in neonates. When prescribing BLINCYTO (with preservative) in neonatal patients, consider the combined daily metabolic load of benzyl alcohol from all sources including BLINCYTO (with preservative). The BLINCYTO 7-Day bag (with preservative) contains 7.4 mg of benzyl alcohol per mL *[see Warnings and Precautions (5.12)]*.

Benzyl alcohol administration may contribute to metabolic acidosis in pediatric patients, particularly those with immaturity of the metabolic pathway for alcohol, or those with underlying conditions or receiving concomitant medications that could predispose to acid base imbalance. Monitor these patients during use of Blincyto (with preservative) for new or worsening metabolic acidosis.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	June 14, 2023
Time period of search	December 3, 2014† - June 13, 2023
Search type	RxLogix PV Reports Quick Query
Product terms	Product Active Ingredient: Blinatumomab
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † Blincyto U.S. approval date Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from December 3, 2014, to June 13, 2023, with blinatumomab.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From December 3, 2014, to June 13, 2023, With Blinatumomab

	All Reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	3,176 (1,814)	2,604 (1,260)	514 (195)
Pediatrics (0 - <18 years)	832‡ (291)	741‡ (205)	200‡ (25)

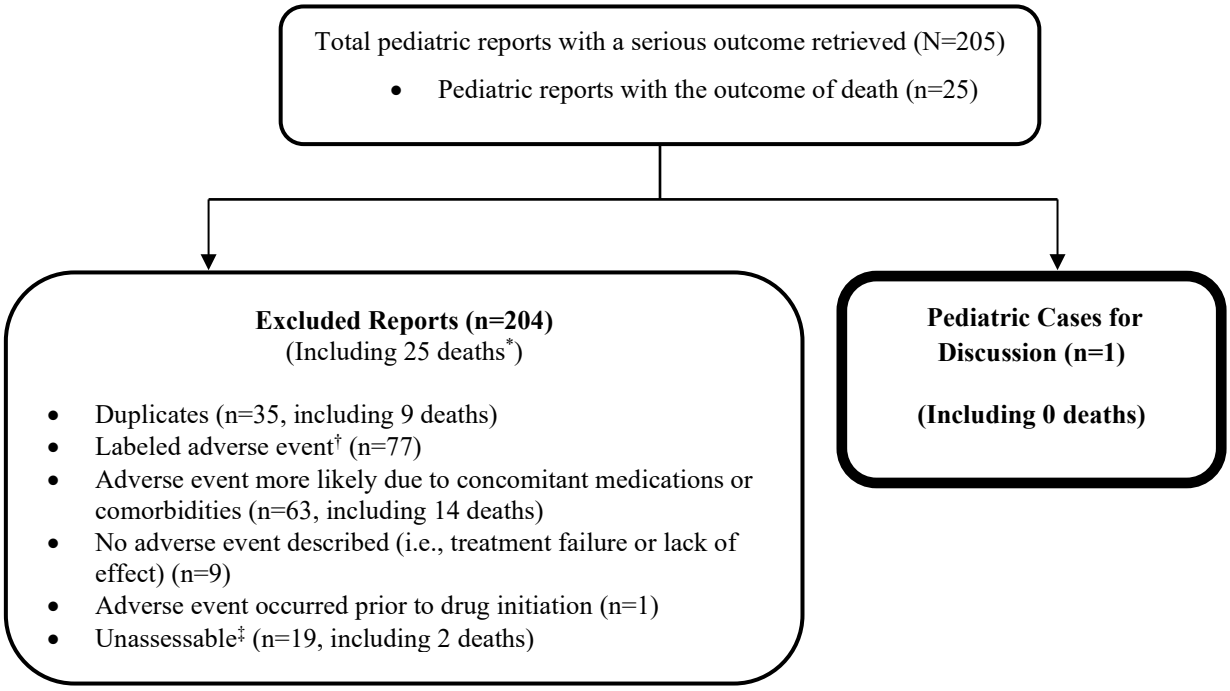
* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
‡ See Figure 1. Two additional reports of U.S. pediatric deaths were identified among reports not reporting an age. These reports are reflected in the counts of pediatric reports.

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 205 U.S. serious pediatric reports from December 3, 2014, to June 13, 2023. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded 204 reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

Appendix B contains a line listing of the one pediatric case in the case series.

Figure 1. Selection of U.S. Serious Pediatric Cases With Blinatumomab



* Twenty-five excluded U.S. FAERS reports described fatal outcomes. None of the deaths were determined to be attributed to blinatumomab. These reports were excluded for the following reasons: nine reports were duplicate reports. In 14 reports, death was likely due to a comorbidity including leukemia progression (n=8), graft versus host disease after transplant (n=2), *E. coli* bacteremia and renal failure (n=1), coronavirus and influenza infection (n=1), secondary to ARDS following possibly due to complications from lumbar puncture (n=1), and adenovirus infection after transplant (n=1). Two reports described a fatal outcome but were unassessable as they contained insufficient details to determine causality, including one report of multiorgan dysfunction with unclear etiology and one report of death with no clinical details provided.

† Labeled adverse event does not represent increased severity or frequency.

‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.3 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=1)

We identified one FAERS case with blinatumomab in the U.S. pediatric population reporting a non-fatal serious outcome. The case is summarized below.

FAERS #19149873, USA, Periodic Report, Other Serious: This case involves a 3-year-old male with Trisomy 21 on blinatumomab during an open-label investigational study for B cell precursor acute lymphoblastic leukemia. The patient's concomitant medications included methotrexate and leucovorin. Approximately 2 weeks after starting blinatumomab, he experienced grade 3 akathisia notable for constant upper and lower extremity movements, sitting up, falling over, kicking, biting, and aggression towards family members. Symptoms were not resolved with any pharmacologic agents such as oxycodone, clonazepam, lorazepam,

diphenhydramine, promethazine, or hydroxyzine. On the 15th day of blinatumomab therapy, blinatumomab was discontinued per the mother's request, and at the time of the report (2 months after the event), the akathisia was reported as resolving.

Reviewer's comment: There is a possible relationship between akathisia and blinatumomab, based on the temporal relationship between akathisia episode and positive dechallenge following blinatumomab discontinuation. However, the case does not provide sufficient details to assess whether the concomitant medications or other underlying medical conditions contributed to the adverse events. DPV performed a search of the FAERS database on August 11, 2023, for reports with the MedDRA Preferred Term Akathisia with blinatumomab in patients of all ages. Additionally, DPV searched the medical literature for publications describing blinatumomab and akathisia. The FAERS and literature searches identified no additional cases describing akathisia with blinatumomab. We do not have sufficient evidence to support a signal of akathisia with blinatumomab at this time.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with blinatumomab in pediatric patients less than 18 years of age from December 3, 2014, to June 13, 2023. Of the 205 reports reviewed, one case was included in our case series. We identified a singular case reporting the unlabeled event of akathisia. The case was possibly related to blinatumomab; however, additional evaluation of the FAERS database and medical literature did not identify sufficient evidence to support a signal of akathisia with blinatumomab at this time.

Overall, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with blinatumomab in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for blinatumomab at this time and will continue routine pharmacovigilance monitoring for blinatumomab.

6 REFERENCES

1. Blincyto (blinatumomab), for injection, for intravenous use [Prescribing Information]. Thousand Oaks, CA: Amgen, Inc.; July 2023.
2. Krauss A. Clincial Review of BLA 125557 S-005 Blincyto (blinatumomab) injection, lyophilized powder. August 2016. https://www.fda.gov/media/124175/download.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=1)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	04/17/2021	19149873	3	US-AMGEN-USACT2021055150	Periodic	3	Male	USA	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those that are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: OT=other medically significant, USA=United States of America

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

OMAYMA A KISHK
10/24/2023 09:13:07 AM

IVONE E KIM
10/24/2023 10:11:00 AM

CARMEN CHENG
10/24/2023 11:44:26 AM

MONICA MUNOZ
10/24/2023 12:51:28 PM