Department of Health and Human Services
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Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	December 22, 2025
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Product Name:	Aranesp (darbepoetin alfa)
Pediatric Labeling Approval Date:	July 23, 2015
Application Type/Number:	BLA 103951
Applicant:	Amgen, Inc.
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Aranesp (darbepoetin alfa) in pediatric patients less than 17 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 darbepoetin alfa in pediatric patients.

Aranesp (darbepoetin alfa) is an erythropoiesis-stimulating agent initially approved in the U.S. on September 17, 2001. Darbepoetin alfa is currently indicated for the treatment of anemia due to:

- Chronic Kidney Disease (CKD) in patients on dialysis and patients not on dialysis.
- The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

This pediatric postmarketing safety review was prompted by pediatric labeling on July 23, 2015, which expanded the use of darbepoetin alfa to include use in pediatric patients 1 month to 16 years old with CKD receiving or not receiving dialysis.

On February 25, 2015, DPV completed an overview of the pediatric safety profile of darbepoetin alfa for all dates through January 20, 2015. No new safety signals were identified. Darbepoetin alfa has not previously been presented to the Pediatric Advisory Committee.

DPV reviewed all U.S. serious FAERS reports with darbepoetin alfa in pediatric patients less than 17 years of age from January 21, 2015, through June 3, 2025, and identified 94 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with darbepoetin alfa in pediatric patients less than 17 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Aranesp (darbepoetin alfa) in pediatric patients less than 17 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 darbepoetin alfa in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Aranesp (darbepoetin alfa) is an erythropoiesis-stimulating agent initially approved in the U.S. on September 17, 2001. Darbepoetin alfa is currently indicated for the treatment of anemia due to:

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1.2 RELEVANT LABELED SAFETY INFORMATION

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

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE

See full prescribing information for complete boxed warning.

Chronic Kidney Disease:

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
- No trial has identified a hemoglobin target level, Aranesp dose, or dosing strategy that does not increase these risks.
- Use the lowest Aranesp dose sufficient to reduce the need for red blood cell (RBC) transfusions.

Cancer:

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
- Use the lowest dose to avoid RBC transfusions.
- Use ESAs only for anemia from myelosuppressive chemotherapy.

----------**CONTRAINDICATIONS**----------

- Uncontrolled hypertension
- Pure red cell aplasia (PRCA) that begins after treatment with Aranesp or other erythropoietin protein drugs
- Serious allergic reactions to Aranesp

----------**WARNINGS AND PRECAUTIONS**----------

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism: Using Aranesp to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with coexistent cardiovascular disease and stroke.
- Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients with Cancer.
- Hypertension: Control hypertension prior to initiating and during treatment with Aranesp.
- Seizures: Aranesp increases the risk for seizures in patients with CKD. Increase monitoring of these patients for changes in seizure frequency or premonitory symptoms.
- PRCA: If severe anemia and low reticulocyte count develop during Aranesp treatment, withhold Aranesp and evaluate for PRCA.
- Serious Allergic Reactions: Discontinue Aranesp and manage reactions.
- Severe Cutaneous Reactions: Discontinue Aranesp.

----------**ADVERSE REACTIONS**----------

- Patients with CKD: Adverse reactions in ≥ 10% of Aranesp-treated patients in clinical studies were hypertension, dyspnea, peripheral edema, cough, and procedural hypotension.
- Patients with Cancer Receiving Chemotherapy: Adverse reactions in ≥ 1% of Aranesp-treated patients in clinical studies were abdominal pain, edema, and thrombovascular events.

----------**USE IN SPECIFIC POPULATIONS**----------

8.4 Pediatric Use

Pediatric Patients with CKD
The safety and effectiveness of Aranesp in pediatric patients with CKD receiving and not receiving dialysis have been established in the age groups 1 month to 16 years old. No data are available in pediatric patients less than 1 month old. Use of Aranesp in these age groups is supported by evidence from adequate and well-controlled studies of Aranesp in adults with additional data from a randomized trial evaluating two schedules (weekly and every 2 week dosing) in 114 pediatric patients 1 to 16 years of age receiving darbepoetin alfa, and an observational registry study in 319 pediatric patients < 1 to 16 years of age receiving darbepoetin alfa. Aranesp safety and efficacy were similar between adults and pediatric patients with CKD receiving and not receiving dialysis when Aranesp was used for initial treatment of anemia or patients were transitioned from treatment with epoetin alfa to Aranesp.

Pediatric Patients with Cancer
The safety and efficacy of Aranesp in pediatric patients with cancer have not been established.

2 METHODS AND MATERIALS

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

Table 1. FAERS Search Strategy*

Date of search	June 4, 2025
Time period of search	January 21, 2015† - June 3, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product Active Ingredient; Darbepoetin alfa
MedDRA search terms (Version 28.0)	All Preferred Terms

* See Appendix A for a description of the FAERS database.
† The FAERS search period for the overview of the pediatric safety profile of darbepoetin alfa review was completed for all dates through January 20, 2015.
Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities

3 RESULTS

3.1 SELECTION OF U.S. SERIOUS PEDIATRIC CASES IN FAERS

Our FAERS search retrieved 94 U.S. serious[a] pediatric reports for patients less than 17 years old from January 21, 2015, through June 3, 2025,[b] including 60 reports with the outcome of death. We excluded all 94 reports from the case series for the reasons described below:

- Duplicate (n=1)
- Labeled adverse event not representing increased severity (n=5)
- Adverse event more likely due to concomitant medications or comorbidities (n=2)
- No adverse event described (i.e., treatment failure or lack of effect) (n=1)
- Unassessable[c] (n=85, including 60 deaths)

Sixty excluded U.S. FAERS reports described fatal outcomes. The 60 death reports described patients from two publications[2,3] of clinical trials including preterm infants. None of the reports had patient-level data to perform a causality assessment.

After excluding reports as described above, zero cases remained for discussion.

3.2 SUMMARY OF U.S. FATAL PEDIATRIC CASES (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.3 SUMMARY OF U.S. SERIOUS NON-FATAL PEDIATRIC CASES (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

[a] 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.
[b] Includes pediatric reports that were identified among reports not coded with an age.
[c] Unassessable reports are those that 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.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with darbepoetin alfa in pediatric patients less than 17 years of age from January 21, 2015, through June 3, 2025, and identified 94 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with darbepoetin alfa in pediatric patients less than 17 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Aranesp (darbepoetin alfa) [package insert]. Thousand Oaks, CA: Amgen; 2024.

2. Bahr TM, Christensen RD, Weaver-Lewis KA, et.al., 2025. A prospective randomized pilot trial comparing weekly vs. biweekly Darbepoetin administration to preterm infants. J Perinatol. 45:951–956.

3. Ohls RK, Das A, Tan S, et.al., 2025. Darbepoetin, Red Cell Mass, and Neuroprotection in Preterm Infants: A Randomized Clinical Trial. JAMA Pediatr. 179(8):836-845.

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.