Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	December 8, 2023
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Product Name:	Mircera (methoxy polyethylene glycol-epoetin beta) injection
Pediatric Labeling Approval Date:	June 7, 2018
Application Type/Number:	BLA 125164
Applicant:	Vifor (International) Inc.
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Mircera (methoxy polyethylene glycol-epoetin beta) injection in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with methoxy polyethylene glycol-epoetin beta in pediatric patients.

Mircera (methoxy polyethylene glycol-epoetin beta) is an erythropoiesis-stimulating agent (ESA), initially approved in the U.S. on November 14, 2007. Methoxy polyethylene glycol-epoetin beta is currently indicated for the treatment of anemia associated with chronic kidney disease (CKD) in:

- Adult patients on dialysis and adult patients not on dialysis
- Pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA

This pediatric postmarketing safety review was stimulated by pediatric labeling on June 7, 2018, for the treatment of anemia associated with CKD in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA.

DPV searched FAERS for all U.S. serious reports with methoxy polyethylene glycol-epoetin beta in pediatric patients less than 18 years of age from November 14, 2007 to October 31, 2023, and identified three reports. However, we excluded all three reports from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with methoxy polyethylene glycol-epoetin beta in pediatric patients less than 18 years of age.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Mircera (methoxy polyethylene glycol-epoetin beta) injection in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with methoxy polyethylene glycol-epoetin beta in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Mircera (methoxy polyethylene glycol-epoetin beta) is an erythropoiesis-stimulating agent (ESA), initially approved in the U.S. on November 14, 2007. Methoxy polyethylene glycol-epoetin beta is currently indicated for the treatment of anemia associated with chronic kidney disease (CKD) in:[1]

- Adult patients on dialysis and adult patients not on dialysis
- Pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA

This pediatric postmarketing safety review was stimulated by pediatric labeling on June 7, 2018, for the treatment of anemia associated with CKD in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA.[2]

A pediatric safety review for methoxy polyethylene glycol-epoetin beta has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The methoxy polyethylene glycol-epoetin beta labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional methoxy polyethylene glycol-epoetin beta 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 (5.1).**
- **No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks (5.1).**
- **Use the lowest Mircera dose sufficient to reduce the need for red blood cell (RBC) transfusions (5.1).**

Cancer:

- **Mircera is not indicated and is not recommended for the treatment of anemia due to cancer chemotherapy. A dose-ranging study of Mircera was terminated early because of more deaths among patients receiving Mircera than another ESA (5.2).**
- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (5.2).**

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

- Uncontrolled hypertension (4).
- Pure red cell aplasia (PRCA) that begins after treatment with Mircera or other erythropoietin protein drugs (4).
- History of serious allergic reactions to Mircera, including anaphylaxis (4).

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

- Hypertension: Control hypertension prior to initiating and during treatment with Mircera (5.3).
- Seizures: Seizures have occurred in CKD patients participating in Mircera clinical studies. Increase monitoring of these patients for changes in seizure frequency or premonitory symptoms (5.4).
- PRCA: If severe anemia and low reticulocyte count develop during Mircera treatment, withhold Mircera and evaluate for PRCA (5.6).
- Serious Allergic Reactions: Discontinue Mircera and manage reactions (5.7).
- Severe Cutaneous Reactions: Discontinue Mircera (5.8).

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

The most common adverse reactions (≥ 10%) are hypertension, diarrhea, nasopharyngitis. (6).

8.4 Pediatric Use

The safety and effectiveness of Mircera for the treatment of anemia due to CKD have been established in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA. The use of Mircera in this pediatric age group is supported by evidence from adequate and well-controlled studies of Mircera in adults and a dose-finding study in 64 pediatric patients 5 to 17 years of age with CKD on hemodialysis. The adverse reaction profile observed in pediatric patients was consistent with the safety profile found in adults. The safety and effectiveness of Mircera have not been established in patients less than 5 years of age *[see Adverse Reactions (6.1) and Clinical Studies (14.2)]*.

The safety and effectiveness of Mircera have not been established in pediatric patients of any age for subcutaneous administration; for treatment of anemia in patients with CKD on peritoneal dialysis; for treatment of anemia in patients with CKD who are not yet on dialysis; and for patients whose hemoglobin level has not been previously stabilized by treatment with an ESA.

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	November 1, 2023
Time period of search	November 14, 2007† - October 31, 2023
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product Active Ingredient: Methoxy Polyethylene Glycol-Epoetin Beta
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † 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

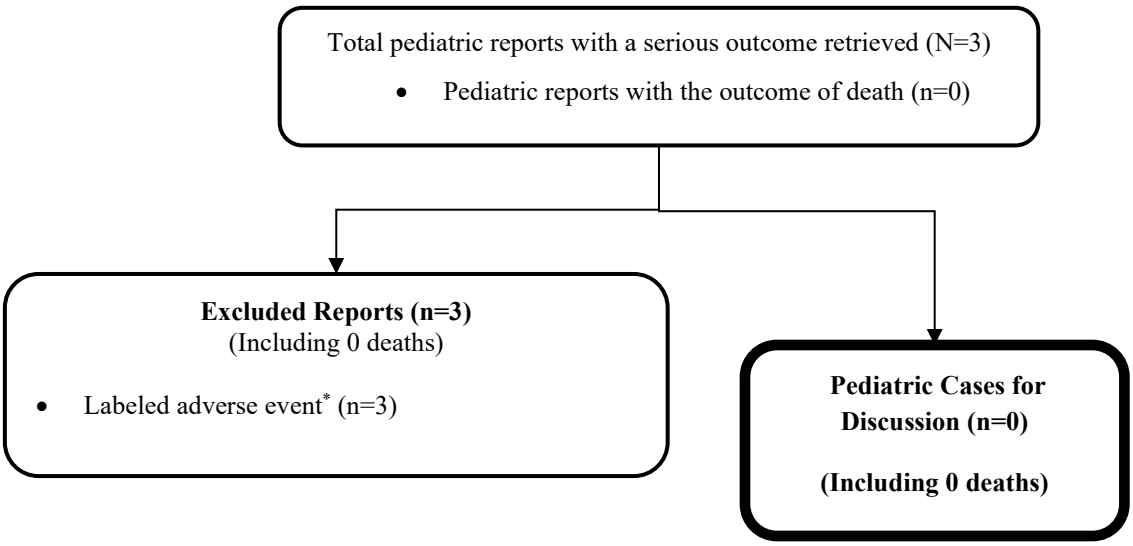
Table 2 presents the number of adult and pediatric FAERS reports from November 14, 2007 to October 31, 2023, with methoxy polyethylene glycol-epoetin beta.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From November 14, 2007 to October 31, 2023 With Methoxy Polyethylene Glycol-Epoetin Beta			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	6,271 (3,469)	4,003 (1,231)	1,234 (137)
Pediatrics (0 - < 18 years)	28 (12)	19 (3)	2 (0)
* 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.			

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

Our FAERS search retrieved three U.S. serious pediatric reports from November 14, 2007 to October 31, 2023. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded three reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of U.S. Serious Pediatric Cases With Methoxy Polyethylene Glycol-Epoetin Beta



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

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=0)

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

4 DISCUSSION

DPV searched FAERS for all U.S. serious reports with methoxy polyethylene glycol-epoetin beta in pediatric patients less than 18 years of age from November 14, 2007 to October 31, 2023, and identified three reports. However, we excluded all three reports from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with methoxy polyethylene glycol-epoetin beta in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for methoxy polyethylene glycol-epoetin beta at this time and will continue routine pharmacovigilance monitoring for methoxy polyethylene glycol-epoetin beta.

6 REFERENCES

1. Mircera (methoxy polyethylene glycol-epoetin beta), for injection, for intravenous or subcutaneous use [Prescribing Information]. Switzerland: Vifor (International) Inc.; March 2023.
2. Schwarsin A. Clincial Review of BLA 125164 S-078 Mircera (methoxy polyethylene glycol-epoetin beta) injection, for intravenous or subcutaneous use. May 2018. https://www.fda.gov/media/114558/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.

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