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:	June 10, 2024
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Product Name:	Repatha (evolocumab) injection
Pediatric Labeling Approval Date:	September 24, 2021
Application Type/Number:	BLA 125522
Applicant:	Amgen, Inc.
TTT Record ID:	2024-9409

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Repatha (evolocumab) injection in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with evolocumab in pediatric patients.

Repatha (evolocumab) injection is a human monoclonal immunoglobulin G2 antibody directed at the proprotein convertase subtilisin/kexin type 9. It was first approved in the United States on August 27, 2015. At initial approval, evolocumab injection was indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease, who require additional lowering of low density lipoprotein cholesterol (LDL-C). It was also approved as an adjunct to diet and other LDL-lowering therapies in patients 13 years and older with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

On December 1, 2017, FDA approved expanding the evolocumab injection indication to include use in adults with established cardiovascular disease to reduce the risk for myocardial infarction, stroke, and coronary revascularization in adults.

On September 24, 2021, FDA approved expanding the indication for evolocumab injection as an adjunct to 1) diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, and 2) other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HoFH, to reduce LDL-C.

This pediatric postmarketing safety review was prompted by pediatric labeling on September 24, 2021, that included a new pediatric indication.

DPV has not previously completed a pediatric postmarketing pharmacovigilance review for evolocumab injection for the Pediatric Advisory Committee.

DPV reviewed all serious FAERS reports with evolocumab injection in pediatric patients less than 17 years of age through May 2, 2024, and identified 19 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 evolocumab injection in pediatric patients less than 17 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Repatha (evolocumab) injection in pediatric patients less than 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with evolocumab in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Repatha (evolocumab) injection is a human monoclonal immunoglobulin G2 antibody directed at the proprotein convertase subtilisin/kexin type 9. It was first approved in the United States on August 27, 2015. At initial approval, evolocumab injection was indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease, who require additional lowering of low density lipoprotein cholesterol (LDL-C). It was also approved as an adjunct to diet and other LDL-lowering therapies in patients 13 years and older with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.[1]

On December 1, 2017, FDA approved expanding the evolocumab injection indication to include use in adults with established cardiovascular disease to reduce the risk for myocardial infarction, stroke, and coronary revascularization in adults.[2]

On September 24, 2021, FDA approved expanding the indication for evolocumab injection as an adjunct to 1) diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, and 2) other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HoFH, to reduce LDL-C.[3]

This pediatric postmarketing safety review was prompted by pediatric labeling on September 24, 2021, that included a new pediatric indication.

DPV has not previously completed a pediatric postmarketing pharmacovigilance review for evolocumab injection for the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The evolocumab injection labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional evolocumab injection labeling information, please refer to the full prescribing information.[3]

> ----------CONTRAINDICATIONS----------
> Patients with a history of a serious hypersensitivity reaction to evolocumab or any of the excipients in REPATHA. (4)
>
> ----------WARNINGS AND PRECAUTIONS----------
> Hypersensitivity Reactions: Angioedema has occurred. If signs or symptoms of serious hypersensitivity reactions occur, discontinue treatment with REPATHA, treat according to the standard of care, and monitor until signs and symptoms resolve. (5.1)

----------ADVERSE REACTIONS----------
Common (> 5% of patients treated with REPATHA and more frequently than placebo) adverse reactions in adults with:
Primary hyperlipidemia: nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions. (6)
Established CVD: diabetes mellitus, nasopharyngitis and upper respiratory tract infection. (6)

8.4 Pediatric Use

The safety and effectiveness of REPATHA in combination with diet and other LDL-C-lowering therapies for the treatment of HoFH have been established in pediatric patients aged 10 years and older. Use of REPATHA for this indication is supported by evidence from an adequate and well-controlled trial in adults and pediatric patients aged 13 years and older with HoFH (including 7 pediatric patients treated with REPATHA) and from open-label studies which included an additional 19 pediatric patients aged 11 years and older with HoFH not previously treated with REPATHA [see Adverse Reactions (6.1) and Clinical Studies (14)].

The safety and effectiveness of REPATHA as an adjunct to diet and other LDL-C-lowering therapies for the treatment of HeFH have been established in pediatric patients aged 10 years and older. Use of REPATHA for this indication is based on data from a 24-week, randomized, placebo-controlled, double-blind trial in pediatric patients with HeFH. In the trial, 104 patients received REPATHA 420 mg subcutaneously once monthly and 53 patients received placebo; 39 patients (25%) were 10 to 11 years of age [see Adverse Reactions (6.1) and Clinical Studies (14)].

The safety and effectiveness of REPATHA have not been established in pediatric patients with HeFH or HoFH who are younger than 10 years old or in pediatric patients with other types of hyperlipidemia.

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	May 3, 2024
Time period of search	All dates through May 2, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: evolocumab
MedDRA search terms (Version 26.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. 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 through May 2, 2024, with evolocumab injection.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through May 2, 2024, With Evolocumab Injection			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	92,057 (88,933)	13,514 (10,506)	983 (815)
Pediatrics (0 - < 17 years)	69‡ (57)	19‡ (7)	3‡ (1)

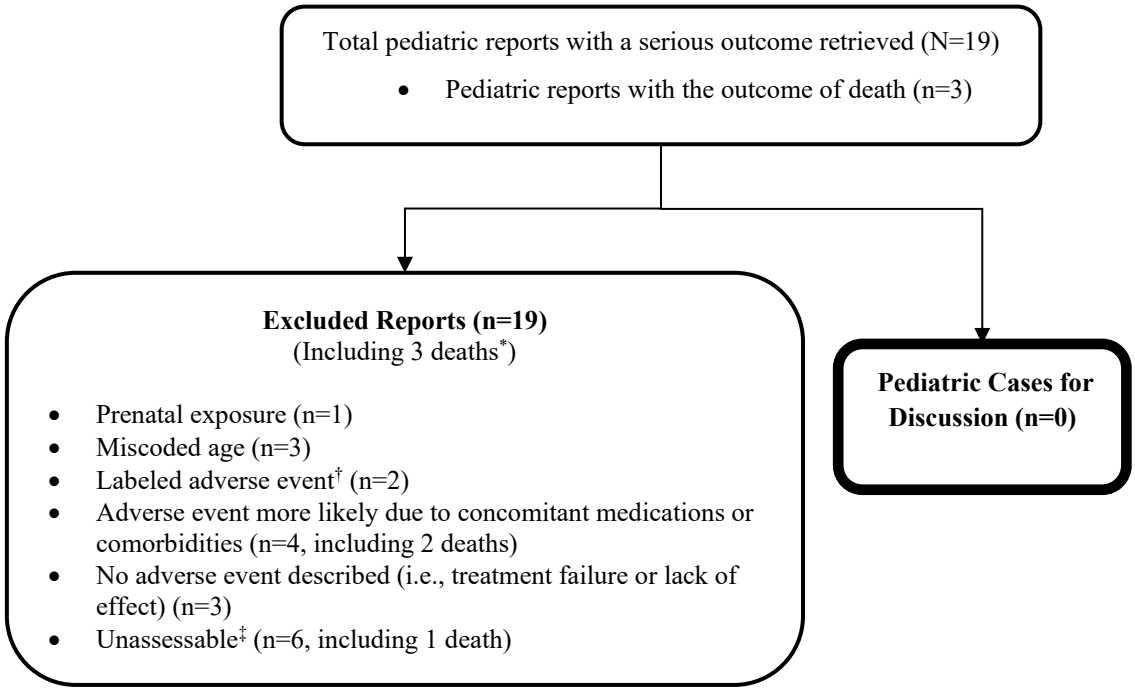
* May include duplicates and transplacental exposures, and have not been assessed for causality

† 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 Serious Pediatric Cases in FAERS

Our FAERS search retrieved 19 serious pediatric reports through May 2, 2024. We reviewed all FAERS pediatric reports with a serious outcome. We excluded all 19 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 Serious Pediatric Cases With Evolocumab Injection



* Three excluded FAERS cases described fatal outcomes. Two cases described patients who died from complications of underlying disease and one case reported a death but did not provide any clinical information to allow for a causality assessment. None of the deaths were determined to be attributed to evolocumab injection.

† 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 Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of Serious Non-Fatal Pediatric Cases (N=0)

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

4 DISCUSSION

DPV reviewed all serious FAERS reports with evolocumab injection in pediatric patients less than 17 years of age through May 2, 2024, and identified 19 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 evolocumab injection in pediatric patients less than 17 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Repatha (evolocumab) injection. [Prescribing information]. Thousand Oaks, CA; Amgen, Inc.: August 2015.
2. Repatha (evolocumab) injection. [Prescribing information]. Thousand Oaks, CA; Amgen, Inc.: December 2017
3. Repatha (evolocumab) injection. [Prescribing information]. Thousand Oaks, CA; Amgen, Inc.: September 2021.

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.