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:	November 8, 2023
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Product Name:	Doptelet (avatrombopag)
Pediatric Labeling Approval Date:	March 21, 2019
Application Type/Number:	NDA 210238
Applicant:	AkaRx, Inc.
TTT Record ID:	2023-6807

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Doptelet (avatrombopag) 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 avatrombopag in pediatric patients.

Doptelet (avatrombopag) is a thrombopoietin receptor agonist that was initially approved in the U.S. on May 21, 2018. Doptelet is currently indicated for the treatment of 1) thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure, and 2) thrombocytopenia in adult patients with chronic immune thrombocytopenia who have had an insufficient response to a previous treatment.

This pediatric postmarketing safety review was prompted by the pediatric labeling on March 21, 2019, that added findings from a juvenile animal toxicity study to subsection 8.4 *Pediatric Use*. The safety and effectiveness of avatrombopag in pediatric patients have not been established.

A pediatric postmarketing pharmacovigilance review for avatrombopag has not been previously presented before the Pediatric Advisory Committee.

DPV searched FAERS for all serious reports with avatrombopag in pediatric patients less than 17 years of age through October 16, 2023, and identified six reports. However, DPV excluded all 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 avatrombopag in pediatric patients less than 17 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Doptelet (avatrombopag) 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 avatrombopag in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Doptelet (avatrombopag) is a thrombopoietin receptor agonist that was initially approved in the U.S. on May 21, 2018. Doptelet is currently indicated for the treatment of 1) thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure, and 2) thrombocytopenia in adult patients with chronic immune thrombocytopenia who have had an insufficient response to a previous treatment.

This pediatric postmarketing safety review was prompted by the pediatric labeling on March 21, 2019, that added findings from a juvenile animal toxicity study to subsection 8.4 *Pediatric Use*. The safety and effectiveness of avatrombopag in pediatric patients have not been established.

A pediatric postmarketing pharmacovigilance review for avatrombopag has not been previously presented before the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

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

> ----------WARNINGS AND PRECAUTIONS----------
> Thrombotic/Thromboembolic Complications: DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease or chronic immune thrombocytopenia. Monitor platelet counts. Monitor for signs and symptoms of thromboembolic events and institute treatment promptly. (5.1)
>
> ----------ADVERSE REACTIONS----------
> In patients with chronic liver disease, the most common adverse reactions (≥ 3%) were pyrexia, abdominal pain, nausea, headache, fatigue, and edema peripheral. (6.1) In patients with chronic immune thrombocytopenia, the most common adverse reactions (≥ 10%) were headache, fatigue, contusion, epistaxis, upper respiratory tract infection, arthralgia, gingival bleeding, petechiae and nasopharyngitis. (6.1)
>
> ----------DRUG INTERACTIONS----------
> Moderate or Strong Dual CYP2C9 and CYP3A4 Inducers or Inhibitors: Dose adjustments are recommended for patients with chronic immune thrombocytopenia. (7.1)
>
> **8.4 Pediatric Use**
> Safety and effectiveness in pediatric patients have not been established.
>
> In a 10-week juvenile toxicology study in rats, avatrombopag was administered at doses ranging from 20 to 300 mg/kg/day. There was no test article-related mortality and there were no clinical signs at doses up to 300 mg/kg/day. In the stomach, dose-dependent degeneration, regenerative

hyperplasia, and atrophy of the glandular epithelium occurred at 100 and 300 mg/kg/day; exposures at 100 mg/kg/day in male rats were 14 times the AUC in patients at the highest recommended dose of 60 mg once daily. An increased incidence of background focal mineralization was also observed in the kidneys of females at 300 mg/kg/day (female rat exposure was 50 times the human exposure based on AUC at the 60 mg daily dose).

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	October 17, 2023
Time period of search	All dates through October 16, 2023
Search type	RxLogix Quick Query
Product terms	Product active ingredient: Avatrombopag, avatrombopag maleate
MedDRA search terms (Version 26.0)	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

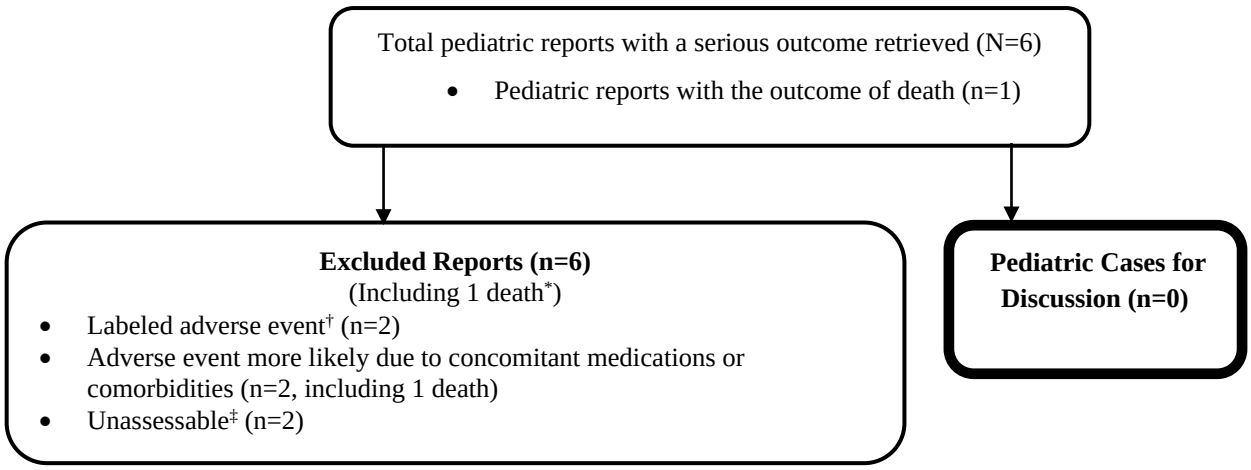
Table 2 presents the number of adult and pediatric FAERS reports through October 16, 2023, with avatrombopag.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA Through October 16, 2023, With Avatrombopag			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	509 (429)	229 (149)	45 (43)
Pediatrics (0 - < 17 years)	6‡ (4)	6‡ (4)	1‡ (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. ‡ See Figure 1. One additional report of pediatric death was identified among reports not reporting an age. This report is reflected in the counts of pediatric reports.			

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved six serious pediatric reports through October 16, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded all six 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 Avatrombopag



* One excluded FAERS report described a fatal outcome. The death was not determined to be attributed to avatrombopag. The report described a 16-year-old female adolescent with a medical history of refractory immune thrombocytopenic purpura (ITP) and trisomy 21 who received avatrombopag for ITP. The patient developed intracranial hemorrhage (ICH) following a presumed fall down the stairs and died from complications of this injury.

† 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 searched FAERS for all serious reports with avatrombopag in pediatric patients less than 17 years of age through October 16, 2023, and identified six reports. However, DPV excluded all 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 avatrombopag in pediatric patients less than 17 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Doptelet (avatrombopag) tablets. [Prescribing information]. Durham, NC; AkaRx, Inc.: June, 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.

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