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: February 17, 2023

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Product Name	**Pediatric Labeling Approval Date**	**Application Type/Number**	**Applicant**
Promacta (eltrombopag olamine) tablet	June 11, 2015	NDA 022291	Novartis
Promacta kit (eltrombopag olamine) oral suspension	August 24, 2015; September 27, 2018	NDA 207027	Novartis

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for eltrombopag in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with eltrombopag in pediatric patients.

Eltrombopag, a thrombopoietin receptor agonist, was initially approved by the FDA on November 20, 2008, as an oral tablet. Eltrombopag is also available as an oral suspension. It is currently indicated:

- for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy
- for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy
- in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia
- for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

This pediatric postmarketing pharmacovigilance review was prompted by three pediatric labeling changes for eltrombopag:

- June 11, 2015: expanded the indication for the treatment of chronic ITP from adults to pediatric patients ages 6 years and older
- August 24, 2015: expanded the indication for the treatment of chronic ITP to include patients aged 1 year and older and a new dosage form (25 mg oral suspension)
- September 27, 2018: new dosage strength of 12.5 mg oral suspension

DPV reviewed all U.S. serious FAERS reports with eltrombopag in the pediatric population (ages 0 – 17 years) from November 20, 2008, through October 20, 2022. We identified two cases reporting unlabeled events of vitreous opacities and pancreatitis. Additional evaluations of reports in the FAERS database did not identify sufficient evidence to support a signal of vitreous opacities or pancreatitis with eltrombopag at this time.

We identified no new safety signals and no deaths directly associated with eltrombopag.

DPV will continue to monitor all adverse events associated with the use of eltrombopag.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for eltrombopag in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with eltrombopag in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Eltrombopag, a thrombopoietin receptor agonist, was initially approved by the FDA on November 20, 2008 as an oral tablet. Eltrombopag is also available as an oral suspension. It is currently indicated:[1]

- for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
- for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.
- in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.
- for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

Table 1 shows the pediatric labeling changes for eltrombopag.

Table 1. Timeline of Pertinent Eltrombopag Pediatric Labeling Changes

Date	Labeling Change
June 11, 2015	• New indication: inclusion of pediatric patients ages 6 years and older as part of the approved indication for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenia who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy[2, 3]
August 24, 2015	• New dosage form: Promacta (eltrombopag) for 25 mg oral suspension[4, 5] • Indication extended: for the treatment of thrombocytopenia in adult and pediatric patients 1 year and older with chronic immune (idiopathic) thrombocytopenia who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy[4, 5]
September 27, 2018	• New dosage strength: 12.5 mg oral suspension[6, 7]
November 16, 2018*	• New indication: Promacta in combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia.[8]

*This labeling change is exempt from the Pediatric Research Equity Act because eltrombopag has orphan drug designation for this indication.

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling changes for eltrombopag on June 11, 2015, August 24, 2015, and September 27, 2018. DPV has not previously presented eltrombopag to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The eltrombopag labeling contains the following safety information excerpted from the Highlights section of the labeling as well as the Pediatric Use subsection.[1] For further labeling information, please refer to the full prescribing information.

WARNING: RISK FOR HEPATIC DECOMPENSATION IN PATIENTS WITH CHRONIC HEPATITIS C and RISK OF HEPATOTOXICITY

See full prescribing information for complete boxed warning.

In patients with chronic hepatitis C, PROMACTA in combination with interferon and ribavirin may increase the risk of hepatic decompensation. (5.1)

PROMACTA may increase the risk of severe and potentially life-threatening hepatotoxicity. Monitor hepatic function and discontinue dosing as recommended. (5.2)

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

- **Hepatotoxicity:** Monitor liver function before and during therapy. (5.2)
- **Increased Risk of Death and Progression of Myelodysplastic Syndromes to Acute Myeloid Leukemia**. (5.3)
- **Thrombotic/Thromboembolic Complications:** Portal vein thrombosis has been reported in patients with chronic liver disease receiving PROMACTA. Monitor platelet counts regularly. (5.4)

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

Across all indications, the most common adverse reactions (≥ 20% in any indication) were: anemia, nausea, pyrexia, alanine aminotransferase increased, cough, fatigue, headache, and diarrhea. (6.1)

8.4 Pediatric Use

The safety and efficacy of PROMACTA have been established in pediatric patients 1 year and older with persistent or chronic ITP and in pediatric patients 2 years and older with IST-naïve severe aplastic anemia (in combination with h-ATG and cyclosporine). Safety and efficacy in pediatric patients below the age of 1 year with ITP have not been established. Safety and efficacy in pediatric patients with thrombocytopenia associated with chronic hepatitis C and refractory severe aplastic anemia have not been established.

The safety and efficacy of PROMACTA in pediatric patients 1 year and older with persistent or chronic ITP were evaluated in two double-blind, placebo-controlled trials *[see Adverse Reactions (6.1), Clinical Studies (14.1)]*. The pharmacokinetics of eltrombopag have been evaluated in 168 pediatric patients 1 year and older with ITP dosed once daily *[see Clinical Pharmacology (12.3)]*. See *Dosage and Administration (2.1)* for dosing recommendations for pediatric patients 1 year and older.

The safety and efficacy of PROMACTA in combination with h-ATG and cyclosporine for the first-line treatment of severe aplastic anemia in pediatric patients 2 years and older were evaluated in a single-arm, open-label trial *[see Adverse Reactions (6.1), Clinical Studies (14.3)]*. A total of 26 pediatric patients (ages 2 to < 17 years) were evaluated; 12 children (aged 2 to < 12 years) and 14 adolescents (aged 12 to < 17). See *Dosage and Administration (2.3)* for dosing recommendations for pediatric patients 2 years and older. The safety and efficacy of PROMACTA in combination with h-ATG and cyclosporine in pediatric patients younger than 2 years for the first-line treatment of severe aplastic anemia have not yet been established. In patients 2 to 16 years of age, 69% of patients experienced serious adverse events compared to 42% in patients 17 years and older. Among the 12 patients who were 2 to 11 years of age in the PROMACTA D1-M6 cohort and reached the 6-month assessment or withdrew earlier, the complete response rate at Month 6 was 8% versus 46% in patients age 12 to 16 years and 50% in patients 17 years of age and older.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 2**.

Table 2. FAERS Search Strategy*	
Date of search	October 21, 2022
Time period of search	November 20, 2008† - October 20, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Product Active Ingredient: Eltrombopag, Eltrombopag olamine
MedDRA search terms (Version 25.0)	All PT terms
* See Appendix A for a description of the FAERS database. †U.S. approval date Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from November 20, 2008, through October 20, 2022, with eltrombopag.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From November 20, 2008, through October 20, 2022 With Eltrombopag

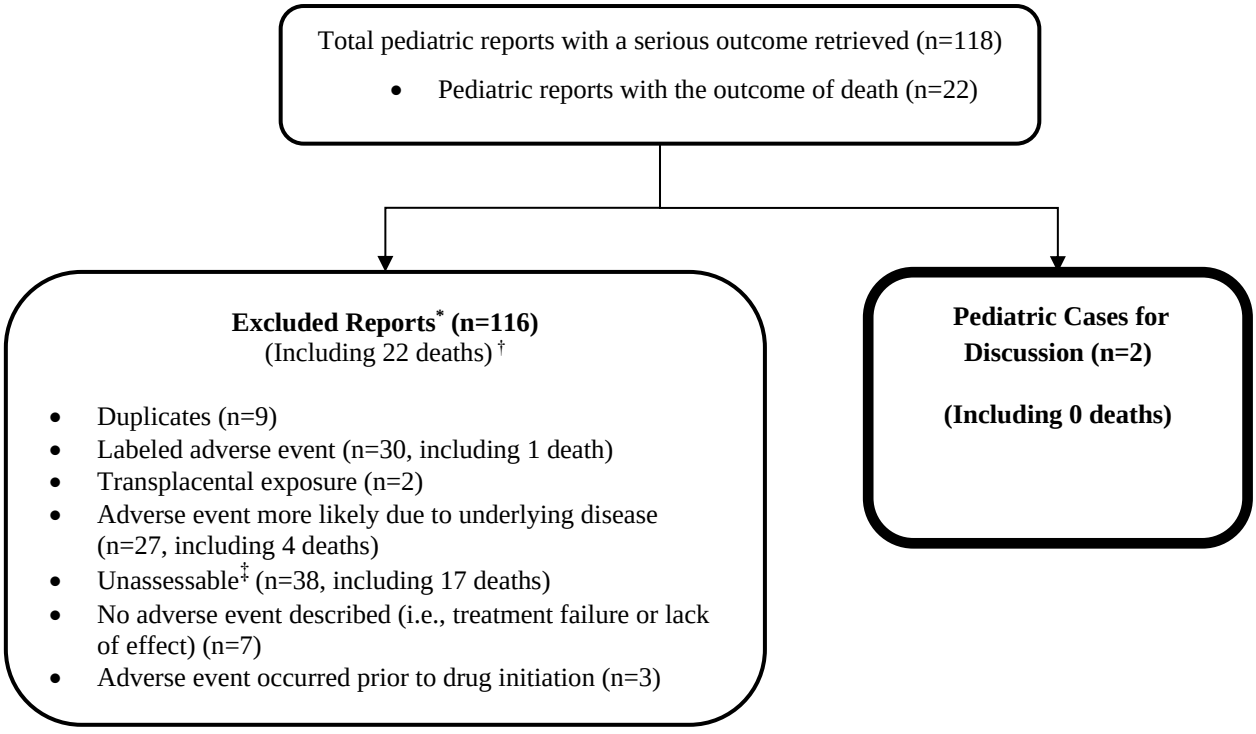
	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	8,910 (4,459)	7,532 (3,126)	2,851 (1,629)
Pediatrics (0 - <18 years)	573‡ (227)	461‡ (118)	79‡ (22)

* 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. Seven additional reports of pediatric deaths were identified among reports not reporting an age. These reports are reflected in the counts for pediatric patients.

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

Our FAERS search retrieved 118 U.S. serious pediatric reports from November 20, 2008, through October 20, 2022. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded 116 reports from the case series for various reasons such as unassessable reports (n=38), labeled adverse event (n=30), adverse event more likely due to underlying disease (n=27), duplicate reports (n=9), no adverse event described (n=7), adverse event occurred prior to eltrombopag initiation (n=3), or transplacental exposure (n=2). **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Eltrombopag



* DPV reviewed these reports, but they were excluded from further discussion for the reasons listed above

† Twenty-two reports described a fatal outcome. One report described a fatal outcome related to a labeled adverse event of thrombosis; however, no clinical details were provided. Four reports described fatal outcomes related to underlying disease (multisystem organ dysfunction, refractory anemia, metastatic central nervous system germ cell tumor, and metastatic Ewings sarcoma). Seventeen reports described fatal outcomes but were unassessable, including fifteen reports with no clinical details, one report of death secondary to "natural causes", and one report of fatal cardiac arrest.

‡ Unassessable: Case 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) or the information is contradictory or information provided in the case cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for further discussion with eltrombopag.

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=2)

We identified two serious FAERS cases with eltrombopag in the U.S. pediatric population reporting a non-fatal serious outcome. The cases are summarized below.

FAERS #8025154 involves a 10-year-old female on eltrombopag for chronic ITP in an open-label and double blind, randomized, placebo-controlled study. Approximately 153 days after starting eltrombopag, the patient complained of "blurry vision." One week later, a slit lamp biomicroscopy showed "grade 1 or mild anterior vitreous opacity just posterior to the lens capsule." However, the ophthalmologist did not believe the vitreous opacity accounted for the patient's complaint of blurry vision. The investigator considered the vitreous opacity to be an asymptomatic finding and eltrombopag's role could not be excluded.

Reviewer's comment: A search of the FAERS database performed on November 21, 2022, for reports with the MedDRA PT "vitreous opacities" in patients of all ages identified no additional cases. Because this is a singular case with missing clinical details (e.g., baseline eye exam, outcome of blurry vision, interventions, and additional symptoms), we do not have sufficient evidence to support a signal of vitreous opacities with eltrombopag at this time.

FAERS #9283682 involves a 12-year-old male on eltrombopag for ITP. He had a past medical history of intracranial hemorrhage and splenectomy and his concomitant medications included penicillin and ferrous sulfate. Fourteen days after starting eltrombopag, the patient was hospitalized for suspected pancreatitis as the patient had elevated amylase and lipase levels of 298 units/L and 4,489 units/L, respectively. The patient's abdominal ultrasound as follow-up test was negative for pancreatitis and eltrombopag was discontinued while the patient was hospitalized.

Reviewer's comment: While the patient's amylase and lipase were elevated upon presentation to the hospital, the follow-up abdominal ultrasound ruled out pancreatitis as the cause. There are not enough clinical details to determine if eltrombopag contributed to the suspected pancreatitis.

A search of the FAERS database performed on November 21, 2022, for reports with the MedDRA PT "pancreatitis" in patients of all pediatric ages identified no additional reports with possible or probable causal association between pancreatitis and eltrombopag. At this time, we do not have sufficient evidence to support a signal of pancreatitis with eltrombopag.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with eltrombopag in the pediatric population (ages 0 – 17 years) from November 20, 2008, through October 20, 2022. We identified two cases reporting unlabeled events of vitreous opacities and suspected pancreatitis. Additional evaluations of the FAERS database did not identify sufficient evidence to support a signal of vitreous opacities or pancreatitis with eltrombopag at this time. We identified no new safety signals and no deaths directly associated with eltrombopag.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for eltrombopag at this time.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of eltrombopag.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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 (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

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 or not 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.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=2)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	07/07/2011	8025154	1	US-GLAXOSMITHKLINE-A0928135A	15-Day	10	Female	USA	OT
	05/27/2011	7964834†	1	A0928135A	15-Day	10	Female	USA	OT
	02/14/2018	14530781†	1	PHHO2011US022431	15-Day	10.869	Female	USA	OT
2	05/10/2013	9283682	3	US-GLAXOSMITHKLINE-A1022349A	15-Day	12	Male	USA	DS, HO, 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 which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.

†Duplicate report

Abbreviations: DS=disability, HO=hospitalization, OT=other medically significant, USA= United States of America

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