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:	July 8, 2024
Reviewers:	Omayma Kishk, PharmD, BCPPS, Safety Evaluator Division of Pharmacovigilance I (DPV-I) Ivone Kim, MD, Medical Officer DPV-I
Team Leader:	Carmen Cheng, PharmD DPV-I
Division Director:	Monica Muñoz, PharmD, PhD, BCPS DPV-I
Product Name:	Pradaxa (dabigatran etexilate) capsule and oral pellet
Pediatric Labeling Approval Date:	June 21, 2021
Application Type/Number:	NDA 022512 (capsule); NDA 214358 (oral pellet)
Applicant:	Boehringer Ingelheim Pharmaceuticals Inc
TTT Record ID:	2024-9079

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Pradaxa (dabigatran etexilate) capsules and oral pellets in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with dabigatran etexilate in pediatric patients.

Pradaxa (dabigatran etexilate) is a direct thrombin inhibitor that was initially approved as a capsule in the U.S. on October 19, 2010. Dabigatran etexilate capsule is currently indicated in the pediatric population:

- For the treatment of venous thromboembolic events (VTE) in pediatric patients 8 to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days
- To reduce the risk of recurrence of VTE in pediatric patients 8 to less than 18 years of age who have been previously treated.

Pradaxa (dabigatran etexilate) oral pellet was initially approved in the U.S. on June 21, 2021. Dabigatran etexilate pellet is currently indicated in the pediatric population:

- For the treatment of VTE in pediatric patients aged 3 months to less than 12 years of age who have been treated with a parenteral anticoagulant for at least 5 days
- To reduce the risk of recurrence of VTE in pediatric patients aged 3 months to less than 12 years of age who have been previously treated.

This pediatric postmarketing pharmacovigilance review was prompted by two pediatric labeling changes for dabigatran etexilate on June 21, 2021:

- Oral capsule: new pediatric indication for the treatment and reduction in risk of recurrence of VTE in pediatric patients 8 to less than 18 years of age
- Oral pellet: new age appropriate pediatric formulation for the treatment and reduction in risk of recurrence of VTE in pediatric patients 3 months to less than 12 years of age.

DPV reviewed all U.S. serious FAERS reports with dabigatran etexilate in pediatric patients less than 18 years of age from October 19, 2010, through April 2, 2024. DPV identified 14 reports; however, all reports were excluded 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 dabigatran etexilate in pediatric patients less than 18 years of age.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Pradaxa (dabigatran etexilate) capsules and oral pellets in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with dabigatran etexilate in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Pradaxa (dabigatran etexilate) is a direct thrombin inhibitor that was initially approved as a capsule in the U.S. on October 19, 2010. Dabigatran etexilate capsule is currently indicated:[1]

- To reduce the risk of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation
- For the treatment of deep venous thromboembolism (DVT) and pulmonary embolism (PE) in adult patients who have been treated with a parenteral anticoagulation for 5-10 days
- To reduce the risk of recurrence of DVT and PE in adult patients who have been previously treated
- For the prophylaxis of DVT and PE in adult patients who have undergone hip replacement surgery
- For the treatment of venous thromboembolic events (VTE) in pediatric patients 8 to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days
- To reduce the risk of recurrence of VTE in pediatric patients 8 to less than 18 years of age who have been previously treated.

Dabigatran etexilate capsule was not indicated for pediatric patients at original approval but that indication was expanded to include pediatric patients on June 21, 2021.

Pradaxa (dabigatran etexilate) oral pellet was initially approved in the U.S. on June 21, 2021. Dabigatran etexilate oral pellet is currently indicated:[2]

- For the treatment of VTE in pediatric patients aged 3 months to less than 12 years of age who have been treated with a parenteral anticoagulant for at least 5 days
- To reduce the risk of recurrence of VTE in pediatric patients aged 3 months to less than 12 years of age who have been previously treated.

This pediatric postmarketing pharmacovigilance review was prompted by two pediatric labeling changes for dabigatran etexilate on June 21, 2021:[3]

- Oral capsule: new pediatric indication for the treatment and reduction in risk of recurrence of VTE in pediatric patients 8 to less than 18 years of age
- Oral pellet: new age appropriate pediatric formulation for the treatment and reduction in risk of recurrence of VTE in pediatric patients 3 months to less than 12 years of age.

A pediatric safety review for dabigatran etexilate has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The dabigatran etexilate labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection for the oral capsules and pellets. For additional dabigatran etexilate labeling information, please refer to the full prescribing information.

1.2.1 Dabigatran etexilate oral capsules[1]

WARNING: (A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS, and (B) SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning

(A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS: Premature discontinuation of any oral anticoagulant, including PRADAXA, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy (2.6, 2.7, 2.8, 5.1).

(B) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with PRADAXA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis (5.3). Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated (5.3).

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

- Active pathological bleeding (4)
- History of serious hypersensitivity reaction to PRADAXA (4)
- Mechanical prosthetic heart valve (4)

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

- Bleeding: PRADAXA can cause serious and fatal bleeding (5.2)
- Bioprosthetic heart valves: PRADAXA use not recommended (5.4)
- Increased Risk of Thrombosis in Patients with Triple-Positive Antiphospholipid Syndrome: PRADAXA use not recommended (5.6)

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

- Most common adverse reactions (> 15%) are gastrointestinal adverse reactions and bleeding (6.1)

8.4 Pediatric Use

The safety and effectiveness of PRADAXA Capsules for the treatment and the reduction in risk of recurrence of venous thromboembolism have been established in pediatric patients 8 to less than 18 years of age. Use of PRADAXA for this indication is supported by evidence from adequate and well-controlled studies in pediatric patients. These studies included an open-label, randomized, parallel-group study and an open-label, single-arm safety study [see Adverse Reactions (6.1) and Clinical Studies (14.4, 14.5)]. Other age-appropriate pediatric dosage forms of dabigatran etexilate are available for pediatric patients less than 8 years of age for these indications.

Safety and effectiveness of PRADAXA Capsules have not been established in pediatric patients with non-valvular atrial fibrillation or those who have undergone hip replacement surgery.

1.2.2 Dabigatran etexilate oral pellets[2]

WARNING: (A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS, and (B) SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning

(A) PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS: Premature discontinuation of any oral anticoagulant, including PRADAXA, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy (2.5, 2.6, 2.7, 5.1).

(B) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with PRADAXA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis (5.3). Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated (5.3).

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

- Active pathological bleeding (4)
- History of serious hypersensitivity reaction to PRADAXA (4)
- Mechanical prosthetic heart valve (4)

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

- Bleeding: PRADAXA can cause serious and fatal bleeding (5.2)
- Bioprosthetic heart valves: PRADAXA use not recommended (5.4)
- Increased Risk of Thrombosis in Patients with Triple-Positive Antiphospholipid Syndrome: PRADAXA use not recommended (5.6)

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

Most common adverse reactions (> 15%) are gastrointestinal adverse reactions and bleeding. (6.1)

8.4 Pediatric Use

The safety and effectiveness of PRADAXA Oral Pellets for the treatment and the reduction in risk of recurrence of venous thromboembolism have been established in pediatric patients less than 12 years of age. Use of PRADAXA Oral Pellets for this indication is supported by evidence from adequate and well-controlled studies in pediatric patients. These studies included an open-label, randomized, parallel-group study and an open-label, single-arm safety study [see Adverse Reactions (6.1) and Clinical Studies (14.1, 14.2)]. Other age-appropriate pediatric formulations of dabigatran etexilate are available for pediatric patients aged 12 years and older for these indications.

Safety and effectiveness of PRADAXA have not been established in pediatric patients with non-valvular atrial fibrillation or those who have undergone hip replacement surgery.

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	April 3, 2024
Time period of search	October 19, 2010† – April 2, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product Active Ingredient: Dabigatran, Dabigatran etexilate, Dabigatran etexilate mesylate
MedDRA search terms (Version 26.1)	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 October 19, 2010, through April 2, 2024, with dabigatran etexilate.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From October 19, 2010 through April 2, 2024, With Dabigatran Etexilate

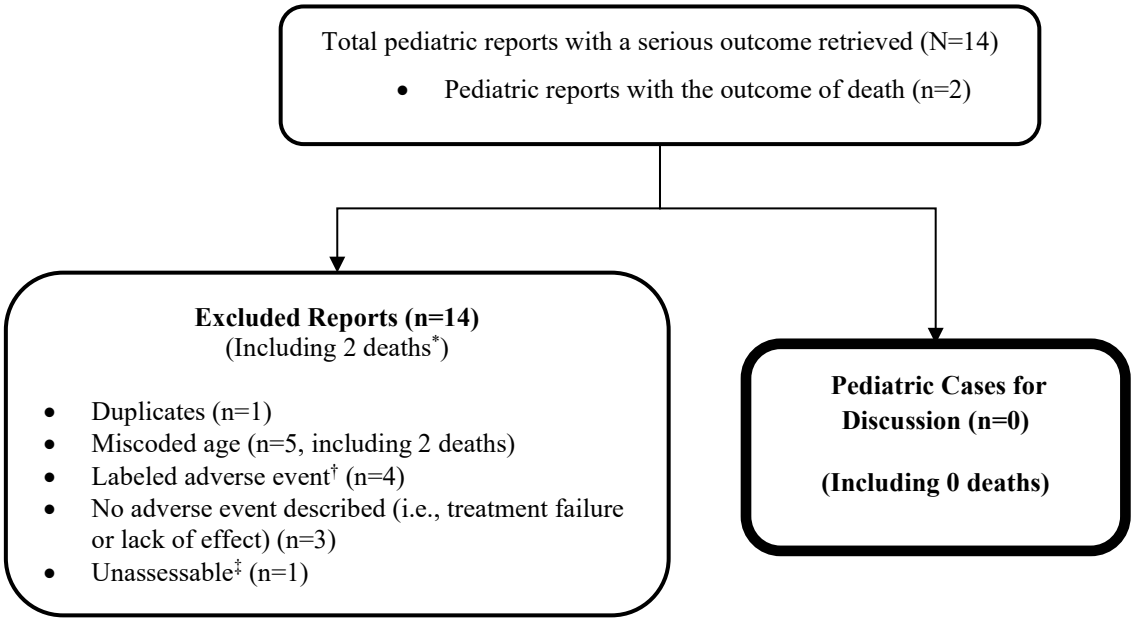
	All Reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	47,547 (24,621)	38,896 (16,163)	7,649 (3,019)
Pediatrics (0 - < 18 years)	58 (20)	49 (14)	7 (2)

* 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 14 U.S. serious pediatric reports from October 19, 2010, through April 2, 2024. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 14 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 Dabigatran Etexilate



* Two excluded U.S. FAERS reports described fatal outcomes. The reports described adult patients miscoded as pediatric patients.
† 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 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 reviewed all U.S. serious FAERS reports with dabigatran etexilate in pediatric patients less than 18 years of age from October 19, 2010, through April 2, 2024. DPV identified 14 reports; however, all reports were excluded 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 dabigatran etexilate in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Pradaxa® (dabigatran etexilate) capsules [Prescribing Information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; November 2023.
2. Pradaxa® (dabigatran etexilate) oral pellets [Prescribing Information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; November 2023.
3. Nossair F. Medical Officer Clinical Review - Amendment of Pradaxa®(dabigatran etexilate) sNDA 022512, S-0041 and NDA 214358. June 2021. https://www.fda.gov/media/151626/download?attachment.

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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