CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214358Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	June 16, 2021
Reviewer:	Kate Gelperin, MD, MPH Division of Epidemiology 1 (DEPI-1)
Through:	Steven Bird, PhD, PharmD, MS, Team Leader DEPI-I
	Simone Pinheiro, ScD, MSc, Director DEPI-I
	Michael Blum, MD, Deputy Office Director Office of Pharmacovigilance and Epidemiology (OPE)
	Sarah Dutcher, PhD, FDA Sentinel Program Lead (designee) Office of Surveillance and Epidemiology (OSE)
	Robert Ball, MD, MPH, Deputy Director OSE
Subject:	ARIA Sufficiency Memo
Drug Name(s):	PRADAXA (dabigatran etexilate)
Application Type/Number:	NDA 214358 (pellets)
Applicant/sponsor:	Boehringer Ingelheim Pharmaceuticals, Inc.
OSE RCM #:	2020-1989

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	
-Exposure	X
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	X

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

Dabigatran etexilate (Pradaxa) was approved for use in the U.S. in 2010, to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Two indications were added for Pradaxa in 2014 for the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days and to reduce the risk of recurrence of DVT and PE in patients who have been previously treated. Dabigatran is a direct thrombin inhibitor. The mechanism of action is competitive direct reversible thrombin inhibition resulting in reduction of thrombin-mediated conversion of fibrinogen to fibrin and thrombin-induced platelet activation, thereby limiting arterial and venous thrombosis. On January 25, 2019 FDA issued a pediatric written request to Boehringer Ingelheim Pharmaceuticals for pediatric studies to investigate the potential use of Pradaxa in the treatment and prophylaxis of venous thromboembolism in pediatric patients. The written request was for studies 1160.106 and 1160.108. Boehringer Ingelheim submitted the following applications in support of the pediatric efficacy of Pradaxa, each application with their respective dosage formulations and proposed indications:

- NDA 022512 / Supplement 041:
  - Marketed dosage formulation: Capsules (75 mg, 110 mg and 150 mg)
  - Proposed dosing regimen: Twice-daily oral administration of actual weight-based (b) (4). The maximum daily dose is (b) (4) mg, divided into two equal doses.
  - Proposed indications:
    - For the treatment of VTE in pediatric patients 8 years of age and older 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 years of age and older who have been previously treated.
- NDA 214358
  - New dosage formulation: Oral pellets (20 mg, 30 mg, 40 mg, 50 mg, 110 mg and 150 mg)
  - Proposed dosing regimen: twice-daily oral administration of actual weight-based and age-based dosing. The maximum daily dose is (b) (4) mg, divided into two equal doses.
  - Proposed indications:
    - For the treatment of venous thromboembolic events (VTE) in pediatric patients 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 less than 12 years of age who have been previously treated.

(b) (4)

(b) (4)

These applications are primarily supported by the results of studies 1160.106 and 1160.108:

- Study 1160.106 is a multi-center, open-label, randomized, active-controlled trial in 267 pediatric patients with image-proven venous thromboembolism (VTE). This trial demonstrated the non-inferiority of Pradaxa, compared to standard of care (SoC) anticoagulation, in the composite primary endpoint of complete thrombus resolution, freedom from recurrent VTE and freedom from VTE-related mortality. With the exception of GI bleeding (9% in the Pradaxa arm vs. 1% in the SoC arm), the overall rate of all other types of bleeding, including all severity sub-groups, was considered by the review team to be comparable between the two treatment arms. This includes major bleeding (2.8% in the Pradaxa arm vs. 2.2% in the SoC arm) and clinically relevant non-major bleeding (1.7% in the Pradaxa arm vs. 1.1% in the SoC arm). GI bleed adverse reactions in the Pradaxa arm were recurrent and occurred at a relatively higher rate in younger pediatric patients.[1]
- Study 1160.108 is a multi-center, open-label, single arm prospective cohort Phase 3 trial in 213 pediatric patients who had a previous history of a treated VTE and have a persistent risk factor for VTE that increases the risk of VTE recurrence. These patients were treated with Pradaxa over a 12-month period for the secondary prevention of VTE. This trial demonstrated a rate of VTE recurrence of 5.1%, which is comparable to rates of pediatric VTE recurrence reported with SoC therapies (7-21%) in published literature.

The clinical reviewer's recommendation on regulatory action is: [2]

- Traditional Approval for NDA 022512/Supplement 041 (capsules) and NDA 214358 (pellets)

(b) (4)

1.2. Describe the Safety Concern

Issues with discrepancy of bioavailability for capsule and pellet formulations

Several issues impacting the optimal pediatric dosing regimen were identified by the clinical pharmacology reviewer and the clinical team. There was discrepancy in the relative bioavailability (BA) of (b) (4) granules (pellets) when compared to capsules between the relative BA study (Study 194) in healthy adults and the population PK analysis performed based on pediatric data. In healthy adults, dabigatran etexilate granules resulted in 37% higher relative BA compared to

[1] CDTL Review; Virginia Kwitkowski; NDA 022512/S-041; Dabigatran etexilate, capsules; 4 March 2021; DARRTS Ref ID 4756897; page 5.

[2] Clinical and Statistical Review; Fadi Nossair; Efficacy supplement NDA 022512/S-041; (b) (4) NDA 214358; Dabigatran etexilate; capsule, oral pellets, (b) (4); 23 February 2021; DARRTS Ref ID 4751663.

dabigatran etexilate capsules. In contrast, the applicant's population PK analysis estimated that the relative BA of dabigatran (b) (4) granules was 38% lower than that for capsules in pediatric population. Given the knowledge gaps and the limitation of data confounding age with formulations, the review team noted a greater uncertainty in the projected exposures based on the population PK analysis and could not rule out the scenario that pediatric patients have similar relative BA (137%) for (b) (4) granules vs capsules as observed in healthy adults. Therefore, in a worst-case scenario, (b) (4) granules could potentially lead to higher exposures than the capsule formulation for the same dose.[3]

Issues with achieving target trough dabigatran concentrations in clinical trials

For each formulation, specific Pradaxa dosing nomograms were utilized in both trials and drug monitoring was implemented to achieve target trough dabigatran concentration of 50-<250 ng/ml, while allowing a single dose adjustment using specific titration nomograms. Due to inability to achieve within-target levels after one dose adjustment, there was a Pradaxa discontinuation rate of 7-12%, with 19-27% of patients needing a dose adjustment due to low trough concentrations, occurring with a significantly higher frequency in younger age groups.

Clinical implications of potential lack of efficacy

Pediatric venous thromboembolism (VTE) is a serious and life-threatening condition. VTE can lead to mortality from pulmonary embolism or morbidity from post-thrombotic syndrome (PTS) or bleeding associated with anticoagulant therapy. PTS is caused by chronic venous insufficiency that develops following VTE, with signs and symptoms including leg pain, vein dilation, edema, skin pigmentation, and venous ulcers. The incidence of PTS can be reduced by timely recognition and treatment and prevention of recurrent VTE. Venous thromboembolism (VTE) is a relatively rare disease in pediatric patients and is generally a secondary complication of other conditions such as indwelling central venous catheter (most common cause), cancer, infection, congenital heart disease, trauma, surgery, renal disease, and inherited or acquired thrombophilia. The goals of treating VTE are to prevent local extension and embolization of the thrombus, aid in resolving the existing thrombus, prevent VTE recurrence, and minimize long-term complications (e.g. PTS).

Reviewer recommendation for drug monitoring vs increased initial dose

To address issues with sub-target trough plasma concentrations the clinical reviewer recommended drug monitoring for pediatric patients, as follows: (*Note: diluted thrombin clotting time [dTT] is directly related to the concentration of dabigatran in plasma; however, the lowest concentration margin of the assay is unclear*)[4]

> "Given the recommended dose modifications for patients receiving capsules and the observed high rate of concentration-based discontinuation in younger patients, drug monitoring with dTT (diluted thrombin time) is necessary for all pediatric age groups to ensure patients on Pradaxa achieve target trough concentration of 50-<250 ng/ml, thus ensuring the safe and effective use of Pradaxa in all pediatric patients. This approach is the same approach used in the two pivotal trials."[5]

The Applicant does not agree with drug monitoring, and instead proposes to address concerns related to sub-target exposure with an increase in the approved starting dose of (b) (4) % from

[3] Clinical and Statistical Review; 23 February 2021; DARRTS Ref ID 4751663; page 33.
[4] Boehringer Ingelheim Clinical Trial Report; BI Trial No.: 1160.106; page 61.
[5] Clinical and Statistical Review; 23 February 2021; DARRTS Ref ID 4751663; page 17.

initial dosing used in the trial (i.e., a universal increase in initial dose for younger patients).[6]

Bleeding risk with proposed higher starting dose in younger patients

In the pivotal trial (Study 1160.106) comparing Pradaxa (n=176) to SoC (n=90) there was a trend to higher rates of major and CRNM (clinically relevant non-major) bleeding with Pradaxa:

- Major (2.8% Pradaxa vs. 2.2% SoC)
- CRNM (1.7% Pradaxa vs. 1.1% SoC)
- Minor (19.3% Pradaxa vs. 23.3% SoC)

The proposed increase of (b) (4)% from initial dosing used in the trial may result in amplification of this trend, if it is truly present. Patients in Study 1160.106 who had dose adjustment due to low trough levels (n=34), had no major bleeds, no CRNM and 23.5% (8/34) had a minor bleed. However, 35% (12/34) discontinued Pradaxa, thus may not have been on the drug for sufficient time to observe bleeding risk.[7] The clinical reviewer concluded that, based on available data, modeling-guided adjustment of initial dosing seems safe but close post-marketing surveillance is essential to detect any safety signals.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

The purpose of this analysis is to provide a detailed clinical descriptive characterization of the safety and effectiveness of dabigatran when administered to pediatric patients using an age and weight-based nomogram to calculate proper dose for the treatment of venous thromboembolisms (VTE) or to reduce the risk of recurrence of VTE. It will describe: 1) bleeding (major and CRNM), 2) post-thrombotic syndrome (PTS), and 3) lack of efficacy during follow-up.

1.5. Effect Size of Interest or Estimated Sample Size Desired

This is an observational prospective real-world use study aiming to characterize safety and effectiveness in clinical practice. The study will have a goal for collection of data on 300 patients.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

[6] NDA 022512 S-041 / NDA 214358 Pradaxa (dabigatran etexilate mesylate); Clinical Update; Fadi Nossair; 16 April 2021; slides 10 and 12

[7] NDA 022512 S-041 / NDA 214358 Pradaxa (dabigatran etexilate mesylate); Clinical Update; Fadi Nossair; 16 April 2021; slides 10 and 12.

The desired population consists of pediatric patients ≤12 years of age who receive Pradaxa (dabigatran etexilate) pellets for the treatment of VTE or to reduce the risk of recurrence of VTE in patients who have been previously treated.

2.2 Is ARIA sufficient to assess the intended population?

Yes. ARIA is sufficient to identify Pradaxa treated pediatric patients.

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure is dabigatran etexilate pellets (20, 30, 40, 50, 110, or 150 mg packets) administered per age and weight-based nomogram.

3.2 Comparator Exposure(s)

Not applicable

3.3 Is ARIA sufficient to identify the exposure of interest?

ARIA is not sufficient to identify the exposure. The pellet formulation is dispensed in packets and administered in various combinations based on age and weight-based dosing recommendations per USPI nomogram (e.g. a 3-year old child weighing 7 to <9 kg should receive one 30 mg packet plus one 40 mg packet twice daily, equivalent to 70 mg twice daily). To adequately describe the exposure, this study requires the ability to calculate average daily dosage, identify changes in average daily dosage (e.g., due to lack of effectiveness, VTE progression, or bleeding), and determine whether the dosage prescribed conforms with recommendations per the dosing nomogram (which requires both weight and age).

4 OUTCOME(S)

4.1 Outcomes of Interest

1) Lack of efficacy defined as: lack of complete response (i.e., image-based contiguous partial response, stable disease or progressive disease), non-contiguous VTE while on treatment, or recurrent VTE while on treatment. This outcome requires medical imaging to confirm response, which is unavailable in claims data.

2) Major bleeding and CRNM bleeding while on treatment. Claims based algorithms are available for major bleeding in adults. It's unclear whether these algorithms would have adequate performance characteristics in all pediatric age ranges. No validated algorithms in pediatric patients are available based on a search of published medical literature.[8] Without validation the performance of any algorithm is unknown. Results of investigations (clinical laboratory) conducted for this outcome, including blood coagulation tests (i.e. activated partial thromboplastin time [aPTT], diluted thrombin time [dTT] or ecarin clotting time [ECT]), are not currently available in Sentinel ARIA.

3) Post thrombotic syndrome (PTS) during follow-up. There is an ICD-10 code for post-thrombotic syndrome (I87.0). It is unknown how these codes will perform to identify this

[8] Nellis ME, Levasseur J, Stribling J, Faustino EVS, Zantek ND, Sheth S, Karam O. Bleeding Scales Applicable to Critically Ill Children: A Systematic Review. Pediatr Crit Care Med. 2019 Jul;20(7):603-607. PMID: 30925573.

outcome in pediatric patients and no validated algorithm is available. This outcome would require validation. Without validation the performance of any algorithm is unknown.

4.2 Is ARIA sufficient to assess the outcome of interest?

ARIA is not sufficient to identify lack of efficacy since medical imaging data is unavailable in Sentinel but will be required to confirm response. Validation studies of major bleeding and PTS would be needed in pediatric patients for ARIA to be sufficient.

5 COVARIATES

5.1 Covariates of Interest

Important covariates include:

1) Patient weight is necessary to evaluate whether administered dose is appropriate per USPI and to determine the impact of patient weight on safety and effectiveness. 2) Relevant past medical and surgical history, with special emphasis on the presence of established VTE risk factors and their timing are necessary to evaluate lack of efficacy. Established VTE risk factors are important covariates with existing codes that may not be consistently captured or recorded (e.g., inherited thrombophilia, malignancy, congenital heart disease, presence of a central venous catheter).

5.2 Is ARIA sufficient to assess the covariates of interest?

ARIA is not sufficient to identify the above covariates of interest.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The intended study design is a prospective observational patient registry with descriptive data analysis.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

ARIA is not sufficient with respect to study design because ARIA only supports retrospective analyses and does not have linkages to disease registries.

7 NEXT STEPS

Secondary data are inadequate, and primary data collection will be needed to address the safety concern. The following PMR will be issued to further study this safety and effectiveness issue:

> Conduct a prospective observational study to characterize the safety and effectiveness of dabigatran oral pellet formulation for the treatment of venous thromboembolism (VTE) and to reduce the risk of recurrence of VTE in pediatric patients < 12 years of age. Submit safety follow-up reports for a minimum of 300 pediatric patients treated for the treatment of VTE or reduction of risk of recurrent VTE with the dabigatran oral pellet formulation. Outcomes of interest include all major and clinically relevant non-major and minor bleeding events, post-thrombotic syndrome (PTS), and lack of efficacy. Provide interval and cumulative summary data and detailed analyses

including patient demographics; dabigatran dose formulation, duration of use, and indication for therapy; results of blood coagulation tests when available; and, outcomes of interest in your interim and final study reports.

Schedule Milestones:

Draft Protocol Submission:	Dec / 2021
Final Protocol Submission:	Jun / 2022
Interim Report #1:	Jun / 2023
Interim Report #2:	Dec / 2023
Interim Report #3:	Jun / 2024
Interim Report #4:	Dec / 2024
Interim Report #5:	Dec/ 2025
Interim Report #6:	Dec / 2026
Final Report Submission:	Jun / 2027

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 2, 2021
To:	Brittany Garr-Colon, MPH Regulatory Project Manager **Division of Nonmalignant Hematology (DNH)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	PRADAXA (dabigatran etexilate) ORAL PELLETS
Dosage Form and Route:	for oral use
Application Type/Number:	NDA 214358
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On January 21, 2019 the Agency issued a Written Request for pediatric studies for PRADAXA (dabigatran etexilate), which was revised on June 22, 2019 (Amendment 1). On September 21, 2020, Boehringer Ingelheim Pharmaecuticals, Inc. submitted for the Agency's review an original New Drug Application (NDA) 214358 for PRADAXA (dabigatran etexilate) ORAL PELLETS. The new dosage form, dabigatran etexilate pellets, provides flexible dosing based on age and body weight. The Applicant proposes the following indication: for the treatment and prophylaxis of venous thromboembolism (VTE) in pediatric patients aged less than 12 years as soon as the child is able to swallow soft food.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Nonmalignant Hematology Products (DNH) on September 28, 2020 and October 22, 2020, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for PRADAXA (dabigatran etexilate) ORAL PELLETS.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on February 3, 2021.

2 MATERIAL REVIEWED

- Draft PRADAXA (dabigatran etexilated) ORAL PELLETS MG and IFU received on September 21, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on February 18, 2021.
- Draft PRADAXA (dabigatran etexilate) ORAL PELLETS Prescribing Information (PI) received on September 21, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on February 18, 2021.
- Approved PRADAXA (dabigatran etexilate) capsules labeling dated July 1, 2020.
- DMEPA Label and Labeling Review for PRADAXA ORAL PELLETS dated February 3, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 2, 2021
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	NDA 214358
Product Name and Strength:	Pradaxa (dabigatran etexilate) oral pellets 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)
FDA Received Date:	February 23, 2021
OSE RCM #:	2020-1990-1
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Boehringer Ingelheim Pharmaceuticals submitted revised container labels and carton labeling for Pradaxa (dabigatran etexilate) oral pellets on February 23, 2021 (Appendix A). The revisions are in response to a recommendation that we made during a previous label and labeling review.[1] We reviewed the revised labels and labeling to determine if they are acceptable from a medication error perspective.

2 DISCUSSION

BIPI implemented most of our recommendations; however, BIPI did not agree with all recommendations and provided their rationale for not accepting or modifying the recommendations as noted below.[2]

1. BIPI disagreed with the recommendation to use the same strength color for the 110 mg and 150 mg capsules and oral pellets. Instead BI proposes to leave 110 mg and 150 mg pellet colors as originally submitted but proposes to implement two new colors for the 40 mg and 50 mg oral pellets that are distinct and different from the 110 mg and 150 mg capsule strength colors (see table below). We find the proposed colors to be acceptable from a

[1] DeGraw, S. Label and Labeling Review for Pradaxa (dabigatran etexilate) NDA 214358. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 03. RCM No.: 2020-1990.
[2] Boehringer Ingelheim Response to FDA Package Labeling Comments. Pradaxa (dabigatran etexilate) oral pellets. NDA 214358. 2021 FEB 23. Available at: \\CDSESUB1\evsprod\nda214358\0009\m1\us\responses.pdf

medication error perspective.

(b) (4)

2. BIPI agreed to include a statement on the container labels and carton labeling to mitigate the inadvertent substitution between the Pradaxa dosage forms; however, they revised our previously recommended statement "(b) (4) to read "Pradaxa oral pellets are NOT substitutable on a mg-to-mg basis with other dabigatran etexilate dosage forms". We find this revision to be acceptable from a medication error perspective.

3. BI disagreed with the recommendation to add a statement after the storage statement to alert users that the desiccant packet should NOT be removed from the aluminum bag because a 6 month in-use stability study demonstrated the pellets in an open bag with the desiccant removed remain stable within the 6 month in-use period. We confirmed with OPQ via email on February 28, 2021 that BIPI's rationale is appropriate. OPQ found BIPI's explanation to be reasonable and as such, we agree that a desiccant statement does not need to be added to the carton labeling.

BIPI also made minor editorial changes to the labels and labeling as described in Appendix B. We did not identify any safety concerns associated with these revisions.

3 CONCLUSION

We conclude the revised container labels and carton labeling are acceptable from a medication error perspective. We have no additional recommendations at this time.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 24, 2021

To: Brittany Garr-Colon, MPH, Regulatory Project Manager, Division of Nonmalignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, (DNH)

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Pradaxa (dabigatran etexilate) oral pellets

NDA: 214358

In response to DNH's consult request dated October 22, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and Instructions for Use (IFU) for the original NDA submission for Pradaxa oral pellets. Per communications by electronic mail with Brittany Garr-Colon on February 18, 2021, OPDP has reviewed the proposed carton and container labeling as well.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (Brittany Garr-Colon) on February 17, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on February 23, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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/s/

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 3, 2021
Requesting Office or Division:	Division of Nonmalignant Hematology (DNH)
Application Type and Number:	NDA 214358
Product Name and Strength:	Pradaxa (dabigatran etexilate) oral pellets 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)
FDA Received Date:	September 21, 2020 and January 14, 2021
OSE RCM #:	2020-1990
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1. REASON FOR REVIEW

Boehringer Ingelheim Pharmaceuticals, Inc. submitted NDA 214358 for Pradaxa (dabigatran etexilate) oral pellets for prophylaxis and treatment of venous thromboembolism events (VTE) in pediatric patients less than 12 years of age. We evaluated the proposed container labels, carton labeling, Prescribing Information (PI), Instructions for Use, and Medication Guide for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND INFORMATION & REGULATORY HISTORY

Pradaxa (dabigatran etexilate) 75 mg and 150 mg capsules were approved under NDA 022512 on October 19, 2010, as a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. On April 4, 2014, supplement 18 was approved which added two new indications: for the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days, and to reduce the risk of recurrence of DVT and PE in patients who have been previously treated. On November 20, 2015, supplement 28 was approved which provided for the registration of the 110 mg capsule strength and a new indication: prophylaxis of DVT and PE in patients who have undergone hip replacement surgery.

On September 21, 2020, in addition to NDA 214358, the Sponsor also submitted NDA 022512/S-041 for Pradaxa (dabigatran etexilate) capsule to propose new indications for prophylaxis and treatment of VTE in pediatric patients aged 8 years and older, (b) (4)

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels, carton labeling, and PI for Pradaxa (dabigatran etexilate) to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the proposed PI noted that proposed pediatric doses were described as "age- and weight-based"; however, upon review of the proposed dosing for pediatric patients ages (b) (4) to 12 years old in Table 2 in Section 2.1, we noted that doses only appeared to vary by weight. We brought this to the attention of the Medical Office (MO) and asked if weight-based dosing only was appropriate for pediatric patients ages (b) (4) to 12 years old. The MO confirmed that weight-based dosing only was appropriate for this age group and agreed that Table 2 may be revised to reflect this. The MO also noted that Clinical Pharmacology had concerns with some of the proposed dosing for pediatric patients as some of the doses are greater than the non-weight-based adult doses (i.e., greater than 150 mg twice daily) and has sent information requests to the Sponsor regarding this concern.

Additionally, we noted that doses for patients of the same weight and age differ among the different dosage forms (i.e., capsules versus oral pellets). We brought this to the attention of the MO and Clinical Pharmacology (CP) reviewer. Per the CP reviewer, "Study 1160.194 conducted in healthy subjects showed at steady state, dabigatran etexilate granules (b) (4) resulted in 37% (b) (4) higher relative bioavailability in healthy adult subjects, respectively, compared to dabigatran etexilate capsules. However, the population PK analysis based on Studies 106/108 showed a lower relative bioavailability estimates for the (b) (4) (b) (4) granules (0.62) relative to the capsule formulation." The CP reviewer is seeking additional clarification from the Sponsor on this issue.

As such, we provide recommendations to improve the clarity of the dosing information but defer to the Clinical team to determine the appropriateness of the proposed doses. Additionally, because of the PK differences between the Pradaxa dosage forms, we recommend including a warning statement in the PI and on the carton labeling to alert users that the different dosage forms are not substitutable on a mg-to-mg basis. See section 4.1 for our recommendations for the PI and section 4.2 for our carton labeling recommendations.

Our review of the Instructions for Use (IFU) identified unclear images and language that may be revised to improve clarity of the information presented. See section 4.1 below for our recommendations for the IFU.

Our review of the Medication Guide determined it is acceptable from a medication error perspective and as such, we have no concerns or recommendations at this time.

In addition to our recommendation to include a mg-to-mg substitution warning on the carton labeling as noted above, our review of the container labels and carton labeling also identified an undefined format for the expiration date as well as language that may be revised to improve clarity on the carton labeling. See section 4.2 below for our recommendations for the Sponsor.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes the proposed Medication Guide is acceptable from a medication error perspective. We defer to Patient Labeling Team for recommendations for the Medication Guide. However, DMEPA concludes that the proposed PI, IFU, container labels, and carton labeling can be improved to increase clarity of important information to promote the safe use of the product. We provide our recommendations for the division in Section 4.1 and recommendations for the Sponsor in Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

A. Highlights
    1. Dosage and Administration
        a. As currently presented, the PI does not indicate that the proposed product is not substitutable on a mg-to-mg basis with Pradaxa capsules or other dabigatran etexilate products. We recommend adding the statement "Pradaxa oral pellets are NOT substitutable on a mg-to-mg basis with other dabigatran etexilate (b) (4)."
        b. We recommend revising the dosing statements to split apart the different age groups (i.e., (b) (4) . For example:
            - Treatment of Pediatric VTE:
                - For pediatric patients (b) (4) to less than (b) (4) years: age- and weight-based dosage, twice daily after at least 5 days of parenteral anticoagulant (2.1)
                - For pediatric patients (b) (4) years to less than 12 years: weight-based dosage, twice daily after at least 5 days of parenteral anticoagulant (2.1)
            - Reduction in the Risk of Recurrence of Pediatric VTE:
                - For pediatric patients (b) (4) to less than (b) (4) years: age- and weight-based dosage, twice daily after previous treatment (2.1)
                - For pediatric patients (b) (4) years to (b) (4) 12 years: weight-based dosage, twice daily after previous treatment (2.1)

B. Full Prescribing Information
    1. Recommended Dose [2.1]
        a. As noted above, we recommend adding the statement "Pradaxa oral pellets are NOT substitutable on a mg-to-mg basis with other dabigatran etexilate (b) (4)."
        b. We recommend revising the 2nd paragraph to reflect that some doses for pediatric patients may be weight-based only and to improve clarity. For example, "The recommended dose of PRADAXA is based on the patient's weight or age and weight as shown in the tables below. Administer

PRADAXA twice daily. Adjust doses according to weight or age and weight as treatment progresses."

2. We recommend revising the title of Table 1 to read "Age- and Weight-Based Pediatric Dosing for Patients Less than (b) (4) Years Old".

3. We recommend revising Table 1 to improve the clarity of the information presented. We recommend reorienting the weight column to start with the lowest weight at the top, to replace the "<" symbol with its intended meaning (i.e., less than), to include units following each number (e.g., 20 mg), and to include the "twice daily" dosing schedule after each dose (e.g., 20 mg twice daily).

4. We recommend revising Table 2 to reflect weight-based dosing only, to orient the weight column starting with the lowest weight at the top, and to improve clarity. For example:

Table 2 Weight-Based Pediatric Dosing for Patients (b) (4) Years to 12 Years Old

Actual Weight (kg)	Dose (mg)	Number of Packets Needed
7 kg to less than 9 kg	70 mg twice daily	one 30 mg packet plus one 40 mg packet twice daily
9 kg to less than 11 kg	(b) (4) mg twice daily	(b) (4) twice daily
11 kg to less than 13 kg	110 mg twice daily	one 110 mg packet twice daily

(b) (4)

Instructions for Use (IFU)

1. As currently presented, the instructions state that Pradaxa may be administered with "soft foods or apple juice". If alternative options to apple juice are appropriate for the administration of Pradaxa pellets, we recommend you state additional liquid options (e.g., water) throughout the IFU.

2. As currently presented, the figures are unlabeled which can cause confusion if users do not have a clear cross-reference between the figures and the corresponding text. We recommend labeling all figures and refer to them in the text as appropriate (i.e., Figure 1) to improve clarity.

3. As currently presented, the figure that accompanies step 2 under both preparation methods does not clearly differentiate between the packets for the oral pellets and the desiccant packet. Please revise this figure to more clearly depict the oral pellets packet and the desiccant packet. Additionally, consider whether different desiccant packaging may be employed to help mitigate the risk of inadvertent ingestion of the desiccant due to confusion between the active drug packets and the desiccant packet.

4.2 RECOMMENDATIONS FOR BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

A. General Comments for All Labels and Labeling
    1. We note that two proposed strengths of the oral pellets overlap with two available strengths of the oral capsules (i.e., (b) (4) mg and (b) (4) mg). As currently presented, the same (b) (4) and (b) (4) colors used to highlight the strengths of the (b) (4) mg capsules and (b) (4) mg capsules are used to highlight different strengths of the oral pellets (i.e., (b) (4) mg and (b) (4) mg). To prevent product strength selection errors, we recommend revising the colors used to highlight the strengths. For example, consider using the (b) (4) color for the packaging for the (b) (4) mg oral pellets as the packaging for the (b) (4) mg capsules, and the (b) (4) color for the packaging for the (b) (4) mg oral pellets as the packaging for the (b) (4) mg capsules.

B. Container Labels – Packet
    1. We recommend removing "((b) (4))" after the storage statement.

C. Carton Labeling – Bag
    1. As currently presented, the Medication Guide statement does not describe how the Medication Guide is provided (e.g., enclosed, accompanied, provided separately). Per 21 CFR 208.24(d), the label should "instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided". For example, revise this statement to read, "DISPENSE WITH ACCOMPANYING MEDICATION GUIDE".

D. Carton Labeling – Bag and Outer Carton

1. In order to mitigate the inadvertent substitution between the Pradaxa dosage forms, we recommend adding the statement "Pradaxa oral pellets are NOT substitutable on a mg-to-mg basis with other dabigatran etexilate [redacted]" on the principal display panel of the aluminum bag and outer carton.

2. We recommend revising the "[redacted]" to improve clarity. For example, revise to read: "Discard unused PRADAXA oral pellets 6 months after first opening the aluminum bag."

3. We recommend adding a statement after the storage statement to alert users that the aluminum bag contains a desiccant that should not be removed. For example, "Do NOT remove the desiccant packet from the aluminum bag."

4. As currently presented, the format for the expiration date is not presented. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

5. To ensure consistency with the Prescribing Information, revise "[redacted] to read "Dosage: see prescribing information. Read the Instructions for Use and Medication Guide prior to administration".

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Pradaxa oral pellets received on September 21, 2020, from Boehringer Ingelheim Pharmaceuticals, Inc.

Table 2. Relevant Product Information for Pradaxa oral pellets	
Initial Approval Date	N/A
Active Ingredient	dabigatran etexilate
Indication	• For the treatment of venous thromboembolic events (VTE) in pediatric patients (b) (4) 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 (b) (4) 12 years of age who have been previously treated
Route of Administration	Oral
Dosage Form	Pellets
Strength	20 mg, 40 mg, 50 mg, 110 mg, and 150 mg (per packet)
Dose and Frequency	**Patients less than (b) (4) Years Old, to Be Administered Twice Daily** (b) (4)

	Patients between (b) (4) Years to <12 Years Old, to Be Administered Twice Daily [redacted] (b) (4)
How Supplied	PRADAXA oral pellets are yellowish in a silver-colored, child-resistant Packets. The Packets are placed in an aluminum bag with a (b) (4) desiccant. PRADAXA pellets are supplied as follows:

Strength	Package	NDC
20 mg	unit of use carton with 1 aluminum bag containing 60 Packets	0597-0425-78
30 mg	unit of use carton with 1 aluminum bag containing 60 Packets	0597-0430-18
40 mg	unit of use carton with 1 aluminum bag containing 60Packets	0597-0435-96
50 mg	unit of use carton with 1 aluminum bag containing 60 Packets	0597-0440-53
110 mg	unit of use carton with 1 aluminum bag containing 60 Packets	0597-0445-87
150 mg	unit of use carton with 1 aluminum bag containing 60 Packets	0597-0450-16

Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in the original package to protect from moisture.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 14, 2020 and February 1, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, "Pradaxa". Our search identified 4 recent previous labeling reviews, and we considered our previous recommendations to see if they are applicable for this current review.

Reviewer	Document Title	Application	Date	RCM No.
DeGraw, S.	Label and Labeling Review for Pradaxa	NDA 022512/S-041	2021 FEB 01	2020-2065
Gao, T.	Label and Labeling Review Memo for Pradaxa	NDA 022512/S-031	2015 AUG 14	2015-1386-1
Gao, T.	Label and Labeling Review for Pradaxa	NDA 022512/S-031	2015 AUG 03	2015-1386
Rutledge, M.	Label and Labeling Review for Pradaxa	NDA 022512/S-028	2015 JUN 10	2015-490

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with post-market medication error data, we reviewed the following Pradaxa labeling submitted by Boehringer Ingelheim Pharmaceuticals, Inc. on September 21, 2020 or January 14, 2021.

- Container Labels
- Carton Labeling
- Prescribing Information – includes Medication Guide and Instructions for Use (no image shown): \\CDSESUB1\evsprod\nda214358\0000\m1\us\proposed.doc

See images of labeling below.

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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