CLINICAL REVIEW - AMENDMENT

Application Type	Efficacy Supplement
Application Number	sNDA 022512, S-0041; [redacted] NDA 214358
Priority or Standard	Priority
Submit Date	9/21/2020
Received Date	9/21/2020
PDUFA Goal Date	6/21/2021
Division/Office	Division of Non-malignant Hematology (DNH)
Reviewer Name	Fadi Nossair
CDTL Name	Virginia Kwitkowski
Division/Office	Division of Nonmalignant Hematology
Amendment Completion Date	6/17/2021
Established/Proper Name	Pradaxa®
(Proposed) Trade Name	Dabigatran etexilate
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Dosage Forms	Capsule, oral pellets [redacted]
Applicant Proposed Dosing Regimen	Twice-daily oral administration of actual weight-based and age-based dosing
Applicant Proposed Indication(s)/Population	For sNDA 022512, S-0041: - For the treatment of venous thromboembolism in pediatric patients 8 years of age and older who have been treated with parenteral anticoagulants for at least 5 days - To reduce the risk of recurrence of venous thromboembolism in pediatric patients 8 years of age and older who have been previously treated [redacted] For NDA 214358: - For the treatment of venous thromboembolism in pediatric patients [redacted] 12 years of age who have been treated with parenteral anticoagulants for at least 5 days To reduce the risk of recurrence of venous thromboembolism in pediatric patients [redacted] 12 years of age who have been previously treated
Recommendation on Regulatory Action	Traditional Approval for sNDA 022512, S-0041 and NDA 214358. [redacted]

Recommended Indication(s) / Population(s) (if applicable)	<u>For sNDA 022512, S-0041</u>: - For the treatment of venous thromboembolism in pediatric patients 8 years 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 venous thromboembolism in adult and pediatric patients 8 years to less than 18 years of age who have been previously treated NDA 214358 (for Pradaxa oral pellets): - For the treatment of venous thromboembolism 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 venous thromboembolism in pediatric patients aged 3 months to less than 12 years of age who have been previously treated.

Evaluation of the Suitability of "Drug Monitoring/Dose Adjustment" Approach

The review team received submissions from the Applicant on 3/18/2021 and 3/19/2021 that constituted a major amendment to the application, resulting in extension of the PDUFA goal date to 6/21/2021. The submissions included data supporting the lack of suitability of a drug monitoring/dose adjustment approach, as the basis for therapeutic dose titration for Pradaxa in pediatric patients with VTE, for the following reasons:

- The presence of significant intra-individual variability in plasma concentrations over time, despite appropriate timing of collection and alignment with collection protocols and procedures. This variability is drug-specific due to the pro-drug nature of dabigatran etexilate and has been extensively described from the adult VTE trial data, further corroborated by findings from the pediatric VTE trial data. This variability results in significant uncertainty in relation to the reliable and valid measurement of dabigatran concentration for the purpose of dose titration.
- The presence of significant inter-individual variability in plasma concentrations obtained through population PK modeling, which was used to guide our recommendations for dose adjustment. This variability was due to a discrepancy in the relative bioavailability (BA) of [redacted] granules 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 dabigatran etexilate capsules. In contrast, the applicant's population PK analysis estimated that the relative BA of dabigatran [redacted] granules was 38% lower than that for capsules in pediatric population. A direct BA comparison of between the [redacted] granules and capsules in the pediatric population was not feasible because the capsule and [redacted] granules were used in different age groups (8 to <18 years, and 0 to <12 years, respectively) with limited PK data available from the age group (8 to <12 years) who could receive either formulation.
- Additional Applicant-derived data analyses and literature review that challenged the ability of the diluted thrombin time (dTT) assay to detect dabigatran plasma concentrations < 50 ng/ml in a reliable and accurate fashion.

After evaluation of the Applicant's submissions, the review team agreed that a drug monitoring/dose adjustment approach, similar to that used in the pediatric trials, may not be adequate to address potential sub-therapeutic treatment in younger pediatric patients with VTE. However, given that the pediatric trials were conducted with a target dabigatran trough concentration between 50 and 250 ng/ml and resulted in confirmation of non-inferiority of Pradaxa, when compared to the standard of care, mirroring these criteria in our dosing recommendation is essential to ensure efficacy of Pradaxa in treating pediatric patients with VTE.

Evaluation of the Suitability of "Population PK-based Starting Dose Adjustment" Approach

As noted in our review, the starting dose nomograms were not suitable for younger pediatric patients because, in trial 1160.106, 47% (22/41) of patients on oral pellets and 36% (5/14) of patients on oral solution had steady-state trough concentrations < 50 ng/mL at Visit 3 measurement (without titration),

in contrast to 6% (7/121) of patients on capsules. In addition, 7% (12/176) of patients on Pradaxa had steady-state trough concentrations < 50 ng/mL after one dose adjustment, thus resulting in discontinuation of Pradaxa, with the majority of patients on oral pellets or oral solution (9/12, 75%). As a result of these findings, the Applicant's starting dose nomograms submitted in the initial labeling proposal reflected a ~20% increase in starting dose. However, population PK simulation using the increased starting dose nomograms showed that ~20% of patients are expected to have trough exposures below 50 ng/mL. These findings support the need to implement a strategy to avoid the predicted frequent under-dosing of pediatric patients, which may lead to lack of efficacy in younger pediatric patients.

To further evaluate the impact of the dose adjustment approach, implemented in trial 1160.106, we conducted a sensitivity analysis, evaluating the percentage of patients that achieved the primary composite endpoint and each of its components, in a variety of sub-populations, as summarized in Table 1. It is important to note that dose adjustments in the trial were between 50 to 100% of the initial dosing. Even though we were not able to observe a difference in efficacy outcomes between the sub-populations analyzed, we are not able to conclude that dose adjustment resulted in amelioration of the lack of efficacy risk, which is potentially associated with having low dabigatran trough concentrations. The reason for this uncertainty is that patients who did have a dose adjustment but did not achieve target trough concentration were discontinued from the Pradaxa arm, resulting in inability to assess their true outcome if they would have continued on the higher dose. As a result, even though an appropriate population PK-based adjustment of the starting dose most likely will address the risk of lack of efficacy associated with the Applicant's proposed initial labeling starting dose, it will continue to be associated with a significant, but much lower, level of uncertainty, in relation to lack of efficacy of Pradaxa in younger children.

Table 1: Summary results of sub-population efficacy endpoint analysis, based on need for dabigatran trough concentration-guided dose adjustment and discontinuation

	Patients having at least one level below target range (n=34)	Patients only needing 1 dose adjustment (n=22)	Patients discontinued after dose adjustment (n=12)	Sensitivity analysis dataset - Pradaxa[1] (n=142)	Full analysis dataset - Pradaxa[2] (n=176)	Full analysis dataset - SOC (n=90)
Primary Composite Endpoint – n (%)	17 (50)	10 (46)	7 (58)	64 (45)	81 (46)	38 (42)
Complete Response[3] – n (%)	17 (50)	10 (46)	7 (58)	64 (45)	81 (46)	38 (42)
Partial Response[3] – n (%)	10 (29)	7 (32)	3 (25)	47 (33)	57 (32)	25 (28)
Stable Disease[3] – n (%)	2 (6)	1 (5)	1 (8)	9 (6)	11 (6)	10 (11)
Progressive Disease[3] – n (%)	0 (0)	0 (0)	0 (0)	5 (4)	5 (3)	4 (4)
VTE Recurrence – n (%)	0 (0)	0 (0)	0 (0)	7 (5)	7 (4)	7 (8)
Post-Thrombotic Syndrome – n (%)	0 (0)	0 (0)	0 (0)	7 (5)	7 (4)	2 (2)
VTE-related Death – n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)

[1] Excludes patients that had any trough < 50 ng/ml, [2] Includes all patients who received at least one dose of Pradaxa, [3] Note that note all patients received appropriate imaging allowing for evaluation of VTE status. The following are percentages of patients who were not evaluable for each examined population: 18% (4/22) of patients only needing 1 dose adjustment, 8% (1/12) of patients discontinued after dose adjustment, 15% (5/34) of patients

having at least one level below target range, 13% (18/142) of sensitivity analysis dataset - Pradaxa, 13% (23/176) of full analysis dataset - Pradaxa, and 14% (13/90) of full analysis dataset - SOC

Given the uncertainty surrounding the use of a drug monitoring/dose adjustment approach and the potential beneficial effect of addressing our concerns about lack of efficacy with the proposed starting dose, the review team agreed to consider further adjustments to the Applicant's proposed starting dosing nomograms, which was based on population PK simulation and was submitted as part of the major amendment submissions. In their proposal, the Applicant considered the lowest limit for age as 3 months because pediatric patients that are younger than 3 months are generally unable to swallow pellets, which was agreeable by the review team. The Applicant's revised starting dose nomogram for the oral pellet formulation is shown in Figure 1 and results in a ~ (b) (4) % increase in starting dose, compared to the starting dose nomogram used in the trials.

		Body weight (Kg)
ge_in_year (year)	ge__month (mon)	(b) (4)
0 02	0 25	
0 08	1	
0 17	2	
0 25	3	
0 33	4	
0 42	5	
0 5	6	
0 58	7	
0 67	8	
0 75	9	
0 83	10	
0 92	11	
1	12	
1 5	18	
2	24	
2 5	30	
3	36	
4	48	
5	60	
6	72	
7	84	
8	96	
9	108	
10	120	
11	132	

Figure 1. Final dosing algorithm for oral pellets
Source: BI Response – Dosing Table.docx

When considering the appropriateness of this approach, we acknowledged the potential additional safety concerns that may result from using a higher starting dose than used in the pediatric trials. This is especially relevant in younger pediatric patients for the following reasons:

- The presence of developmental hemostasis in the younger age group, resulting in an increased sensitivity to anti-coagulants and a higher risk of tipping the balance towards bleeding.
- The majority of younger pediatric patients with VTE have complex medical conditions, which predisposes them to having other risk factors for bleeding complications.
- Even though pediatric bleeding AEs were similar to adult bleeding AEs, there was a trend toward higher bleeding AEs observed in younger pediatric patients, which were mostly mild in severity.

Consequently, we concluded that any increase in starting dosing, from the dosing approach used in the trials, should be followed closely in the post-marketing setting. However, to inform the safety

evaluation of the Applicant's proposed dosing for oral pellets, we examined the rate of major, clinically relevant non-major (CRNM) and minor bleeding, as summarized in Table 2. Analysis of patients who received a higher dose secondary to low dabigatran trough concentration with initial trial dosing showed no events of major or CRNM bleeding, with a mild increase in minor bleeding rates. However, even though these findings support the safety of increasing the starting dose of the oral pellet formulation, there remains some uncertainty given that 35% (12/34) of these patients had premature discontinuation of Pradaxa due to persistently lower trough concentration despite single dose adjustment, thus may not have sufficiently long exposure to experience a significant bleeding event.

Table 2: Summary results of sub-population safety endpoint analysis, based on need for dabigatran trough concentration-guided dose adjustment, age stratum and formulation used

	Patients with 1 Dose Titration (n=34)	Stratum 1 – 12 to <18 yrs (n= 111)	Stratum 2 & 3 - < 12 yrs (n=65)	Patients Receiving Capsules (n=121)	Patients Receiving Non-Capsule Formulation (n=55)	Full analysis dataset - Pradaxa[1] (n=176)	Full analysis dataset - SOC (n=90)
Major Bleeding – n (%)	0 (0)	2 (1.8)	2 (3.1)	3 (2.5)	1 (1.8)	4 (2.3)	2 (2.2)
CRNM Bleeding – n (%)	0 (0)	2 (1.8)	0 (0)	2 (1.7)	0 (0)	2 (1.1)	1 (1.1)
Minor Bleeding – n (%)	8 (24)	21 (19)	12 (19)	23 (19)	10 (18)	33 (19)	21 (23)

[1] Includes all patients who received at least one dose of Pradaxa

Through FDA-direct population PK simulation, which was compared to population PK simulation provided by the Applicant, the review team was able to provide scientific recommendations for dose adjustment of the proposed starting doses for the oral pellet formulation, which were generally in alignment with the Applicant's proposal in Figure 1. The final starting doses for the oral pellet formulation, outlined below in Table 3 and Table 4, minimized the percentage of younger pediatric patients with < 50 ng/ml to a level comparable to those observed in older pediatric patients. In addition, the percentage of younger pediatric patients with > 250 ng/ml remained low, even under conditions assuming higher relative BA for the oral pellet formulation. Details of the population PK simulation results, which led to the final agreed-upon starting dosing recommendations for the oral pellet formulation, are available in the clinical pharmacology review.

Table 3: Age- and Weight-Based Dosing for PRADAXA Oral Pellets for Pediatric Patients less than 2 Years Old

Actual Weight (kg)	Age (in months)	Dose (mg) twice daily	Number of Packets Needed
3 kg to less than 4 kg	3 to less than 6 months	30 mg	one 30 mg packet twice daily
4 kg to less than 5 kg	3 to less than 10 months	40 mg	one 40 mg packet twice daily
5 kg to less than 7 kg	3 to less than 5 months	40 mg	one 40 mg packet twice daily
	5 to less than 24 months	50 mg	one 50 mg packet twice daily
7 kg to less than 9 kg	3 to less than 4 months	50 mg	one 50 mg packet twice daily

Actual Weight (kg)	Age (in months)	Dose (mg) twice daily	Number of Packets Needed
	4 to less than 9 months	60 mg	two 30 mg packets twice daily
	9 to less than 24 months	70 mg	one 30 mg packet plus one 40 mg packet twice daily
9 kg to less than 11 kg	5 to less than 6 months	60 mg	two 30 mg packets twice daily
	6 to less than 11 months	80 mg	two 40 mg packets twice daily
	11 to less than 24 months	90 mg	one 40 mg packet plus one 50 mg packet twice daily
11 kg to less than 13 kg	8 to less than 18 months	100 mg	two 50 mg packets twice daily
	18 to less than 24 months	110 mg	one 110 mg packet twice daily
13 kg to less than 16 kg	10 to less than 11 months	100 mg	two 50 mg packets twice daily
	11 to less than 24 months	140 mg	one 30 mg packet plus one 110 mg packet twice daily
16 kg to less than 21 kg	12 to less than 24 months	140 mg	one 30 mg packet plus one 110 mg packet twice daily
21 kg to less than 26 kg	18 to less than 24 months	180 mg	one 30 mg packet plus one 150 mg packet twice daily

Table 4: Weight-Based Dosing for PRADAXA Oral Pellets for Pediatric Patients between 2 Years to less than 12 Years Old

Actual Weight (kg)	Dose (mg) twice daily	Number of Packets Needed
7 kg to less than 9 kg	70 mg	one 30 mg packet plus one 40 mg packet twice daily
9 kg to less than 11 kg	90 mg	one 40 mg packet plus one 50 mg packet twice daily
11 kg to less than 13 kg	110 mg	one 110 mg packet twice daily
13 kg to less than 16 kg	140 mg	one 30 mg packet plus one 110 mg packet twice daily
16 kg to less than 21 kg	170 mg	one 20 mg packet plus one 150 mg packet twice daily
21 kg to less than 41 kg	220 mg	two 110 mg packets twice daily
41 kg or greater	260 mg	one 110 mg packets plus one 150 mg packet twice daily

The Final Post-Marketing Safety Plan

To address the remaining minimal but significant uncertainty, which relates to the efficacy and safety of the use of Pradaxa in patients receiving the oral pellet formulation, we utilized the following post-marketing regulatory tools:

- Implementation of a post-marketing requirement (PMR) that was agreed upon by the Applicant as follows:
  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

- Implementation of enhanced pharmacovigilance (EPV) by requesting the following from the Applicant:
  For a period of five years from the U.S. approval date, submit all reported events of major and clinically relevant non-major (CRNM) bleeding, post-thrombotic syndrome (PTS), and lack of efficacy with Pradaxa (dabigatran etexilate) in pediatric patients ≤12 years of age as 15-day expedited reports, and that you provide detailed analyses of these events in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should include: an analysis of the interval and cumulative adverse event reports (for bleeding, PTS or lack of efficacy) in your post-market safety database; and medical literature reviews for case reports/case series of major and CRNM bleeding events and PTS reported with Pradaxa (dabigatran etexilate).

<u>*Reviewer comments*</u>: We believe that the implementation of the two post-marketing actions will ensure the timely and comprehensive collection of post-marketing data to evaluate and determine the safety profile of the real-world use of Pradaxa oral pellets in pediatric patients. Furthermore, we will work closely with the Applicant to ensure appropriate definitions are applied and comprehensive data collection tools are used to capture all relevant details, in both the PMR study and the EPV reporting.

Post-Marketing Commitment to Address Desiccant-related Dosing Errors

The oral pellet formulation of Pradaxa is supplied in packets, which are contained in an aluminum pouch. The aluminum pouch contains a desiccant packet to guarantee adequate drug product quality over the intended shelf life of 36 months at room temperature. However, the desiccant packet is similar in appearance to the pellet packets, resulting in a potential source of dosing error.

(b) (4)

The Applicant has expressed their commitment to "change the current style of the desiccant from a packet to a unique style (i.e., cylinder format), which differs from the current oral pellets packaging". The change to a unique style desiccant container will ensure differentiation between the two types of containers and their content, thus avoiding any confusion during the drug administration process. As a result, the following post-marketing commitment (PMC), agreed upon by the Applicant, will be implemented:

> *Develop a desiccant container for the Pradaxa oral pellets with a style that differs from the current oral pellets packaging to help mitigate the risk of patients confusing the drug packet with the desiccant. Assess the impact of the new desiccant on the drug product critical quality attributes to ensure that there is no impact on drug product quality and provide corresponding justification (e.g. stability data) in a supplement to be classified in accordance with current FDA guidance.*
>
> Schedule Milestones:
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> Submission date: Jan / 2022

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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