CLINICAL UPDATE

Brand Name	Pradaxa®
Generic Name	dabigatran etexilate
Drug Manufacturer	Boehringer Ingelheim Pharmaceuticals, Inc.

Clinical Update

TYPE OF CLINICAL UPDATE

New Dosage Form, Expanded Indication

FDA APPROVAL DATE

June 21, 2021

LAUNCH DATE

February 16, 2023

REVIEW DESIGNATION

Priority

TYPE OF REVIEW

Type 3 - New Dosage Form; New Drug Application (NDA): 214358

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Pradaxa® Oral Pellets are a direct thrombin inhibitor indicated:

- For the treatment of venous thromboembolic events (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.

MECHANISMS OF ACTION

Dabigatran and its acyl glucuronides are competitive, direct thrombin inhibitors. Because thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited by the active moieties.

DOSAGE FORM(S) AND STRENGTH(S)

Oral Pellets: 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg per packet.

DOSE & ADMINISTRATION

Treatment of Pediatric Venous Thromboembolic Events (VTE):

- For pediatric patients aged 3 months to less than 2 years: age- and weight-based dosage, twice daily after at least 5 days of parenteral anticoagulant.
- For pediatric patients 2 years to less than 12 years: weight-based dosage, twice daily after at least 5 days of parenteral anticoagulant

Reduction in the Risk of Recurrence of Pediatric VTE:

- For pediatric patients aged 3 months to less than 2 years: age- and weight-based dosage, twice daily after previous treatment.
- For pediatric patients aged 2 years to less than 12 years: weight-based dosage, twice daily after previous treatment.

Table 1. 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
	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

Table 1. 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**
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 2. 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

EFFICACY

Treatment of VTE in Pediatric Patients

The DIVERSITY study was conducted to demonstrate the efficacy and safety of Pradaxa® compared to standard of care (SOC) for the treatment of venous thromboembolism (VTE) in pediatric patients from birth to less than 18 years of age. The study was designed as an open-label, randomized, parallel-group, noninferiority study. Patients enrolled were randomized according to a 2:1 scheme to either an age-appropriate formulation (capsules, oral pellets, or oral solution) of Pradaxa® (doses adjusted for age and weight) after at least 5 days and no longer than 21 days of treatment with a parenteral anticoagulant, or to SOC comprised of low molecular weight heparins (LMWH) or vitamin K antagonists (VKA) or fondaparinux. For patients on Pradaxa®, drug concentration was determined prior to the 7th dose and a single titration was permitted to achieve drug target levels of 50 – 250 ng/ml. Inability to achieve target, after one up-titration, resulted in premature termination of study drug in 12 patients (6.8%).

The median treatment duration during the treatment period was 85 days. In total, 267 patients entered the study (leading index VTE was 64% deep vein thrombosis, 10% cerebral venous thrombosis or sinus thrombosis, and 9.0% pulmonary embolism), with 18% of patients having a central line-associated thrombosis. The patient population was 49.8% male, 91.8% white, 4.9% Asian, and 1.5% black; 168 patients were 12 to <18 years old, 64 patients 2 to <12 years, and 35 patients were younger than 2 years. The concomitant VTE-related risk factors of patients in this trial among study arms were as follows: inherited thrombophilia disorder (Pradaxa®: 20%; SOC: 22%), congenital heart disease (Pradaxa®: 12%; SOC: 30%), heart failure (Pradaxa®: 3%; SOC: 18%), history of cancer (Pradaxa®: 10%; SOC: 1%), CVL insertion (Pradaxa®: 23%; SOC: 27%), immobility (Pradaxa®: 13%; SOC: 10%) and significant

infection (Pradaxa®: 15%; SOC: 13%). The number of patients taking concomitant medications with hemostatic effects were similar in both treatment groups (Pradaxa®: 15%; SOC 16%).

The efficacy of Pradaxa® was established based on a composite endpoint of patients with complete thrombus resolution, freedom from recurrent venous thromboembolic event, and freedom from mortality related to venous thromboembolic event (composite primary endpoint). Of the 267 randomized patients, 81 patients (45.8%) in the dabigatran etexilate group and 38 patients (42.2%) in the SOC group met the criteria for the composite primary endpoint. The corresponding rate difference and 95% CI was -0.038 (-0.161, 0.086) and thus demonstrated non-inferiority of Pradaxa® to SOC, since the upper bound of the 95% CI was lower than the predefined non-inferiority margin of 20%.

Table 3. Efficacy Results [ITT population] DIVERSITY Study

	Pradaxa®	Standard of Care
Number of patients randomized (%)	177 (100.0)	90 (100.0)
Complete thrombus resolution	81 (45.8)	38 (42.2)
Freedom from recurrent VTE	170 (96.0)	83 (92.2)
Freedom from mortality related to VTE	177 (100.0)	89 (98.9)
Composite endpoint met	81 (45.8)	38 (42.2)
Difference in rate (95% CI)[1]	-0.038 (-0.161, 0.086)	
p-value for non-inferiority	<0.0001	
p-value for superiority	0.2739	

[1] Mantel-Haenszel weighted difference with age group as stratification factor

Subgroup analyses showed that there were no outliers in the treatment effect for the subgroups by age, sex, region, and presence of certain risk factors (central venous line, congenital heart disease, malignant disease). For the 3 different age strata, the proportions of patients that met the efficacy endpoint in the Pradaxa® and SOC groups, respectively, were 13/22 (59.1%) and 7/13 (53.8%) for patients from birth to < 2 years [Rate Difference -0.052; (95%CI -0.393, 0.288)], 21/43 (48.8%) and 12/21 (57.1%) for patients aged 2 to < 12 years [Rate Difference 0.083; (95%CI -0.176, 0.342)], and 47/112 (42.0%) and 19/56 (33.9%) for patients aged 12 to < 18 years [Rate Difference -0.080; (95%CI -0.234, 0.074)].

Reduction in the Risk of Recurrence of VTE in Pediatric Patients

Study 2 was an open-label, single-arm safety study to assess the safety of Pradaxa® for the prevention of recurrent VTE in pediatric patients from birth to <18 years. Patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY study were included in the study. Eligible patients received age- and weight-adjusted doses of an age-appropriate formulation (capsules or oral pellets) of Pradaxa® until the clinical risk factor resolved, or up to a maximum of 12 months. The primary endpoints of the study included the recurrence of VTE, major and minor bleeding events, and mortality (overall and related to thrombotic or thromboembolic events) at 6 and 12 months.

Of the 214 patients in the study, 162 patients were 12 to <18 years old, 43 patients were 2 to <12 years old, and 9 patients were aged 6 months to <2 years old.

The overall probability of being free from recurrence of VTE during the on-treatment period was 0.990 (95% CI: 0.960, 0.997) at 3 months, 0.984 (95% CI: 0.950, 0.995) at 6 months, and 0.984 (95% CI: 0.950, 0.995) at 12 months. The probability of being free from bleeding events during the on-treatment period was 0.849 (95% CI: 0.792, 0.891) at 3 months, 0.785 (95% CI: 0.718, 0.838) at 6 months, and 0.723 (95% CI: 0.645, 0.787) at 12 months. No on-treatment deaths occurred.

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