Pradaxa® (dabigatran etexilate) – New formulation approval, new indication

- On June 22, 2021, the FDA announced the approval of Boehringer Ingelheim's Pradaxa (dabigatran) oral pellets, 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 and 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.

- Pradaxa was previously approved as an oral capsule. In addition to the approval of the oral pellets, the FDA also approved the capsules for the treatment of 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 and 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 capsules were previously approved:

    - To reduce the risk of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation
    - For the treatment of deep venous thrombosis (DVT) and pulmonary embolism in adult patients who have been treated with a parenteral anticoagulant for 5 to 10 days
    - To reduce the risk of recurrence of DVT and pulmonary embolism in adult patients who have been previously treated
    - For the prophylaxis of DVT and pulmonary embolism, in adult patients who have undergone hip replacement surgery.

- Pradaxa is the first FDA-approved blood thinning medication that children can take orally.

- The approval of Pradaxa for treatment of VTE in pediatric patients was based on DIVERSITY, an open-label, randomized, noninferiority study in 267 pediatric patients from birth to less than 18 years of age. Patients were randomized according to either an age-appropriate formulation 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 standard of care (SOC) comprised of low molecular weight heparins or vitamin K antagonists or fondaparinux. The primary composite endpoint was complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality related to VTE.

    - Of the 267 randomized patients, 81 patients (45.8%) in the Pradaxa group and 38 patients (42.2%) in the SOC group met the criteria for the composite primary endpoint (difference in rate: -0.038, 95% CI: -0.161, 0.086). Non-inferiority of Pradaxa to SOC was met ($p < 0.0001$), since the upper bound of the 95% CI was lower than the predefined non-inferiority margin of 20%.

- The approval of Pradaxa for reduction in the risk of recurrence of VTE in pediatric patients was based on an open-label, single-arm safety study in 214 pediatric patients from birth to less than 18 years of age. 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. 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.

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  - 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.

- Pradaxa carries boxed warnings for premature discontinuation of Pradaxa increases the risk of thrombotic events and spinal/epidural hematoma.

- Pradaxa is contraindicated in patients with:

  - Active pathological bleeding
  - History of a serious hypersensitivity reaction to dabigatran, dabigatran etexilate, or to one of the excipients of the product
  - Mechanical prosthetic heart valve.

- The recommended dosing for Pradaxa in pediatric patients is based on the patient's age and actual weight. Pradaxa is administered twice daily.

  - Refer to the Pradaxa drug labels for complete pediatric dosing and administration recommendations and the Pradaxa capsule drug label for dosing in adults.
  - There are differences between the dosage formulations of Pradaxa with respect to dosing due to differences in bioavailability. Do not substitute different dosage formulations on a milligram-to-milligram basis and do not combine more than one dosage formulation to achieve the total dose.

- Boehringer Ingelheim's launch plans for Pradaxa oral pellets are pending. Pradaxa oral pellets will be available as a 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, and 150 mg strength per packet.