WHAT IS PRADAXA?
• PRADAXA is a prescription anticoagulant (also known as a blood thinner) approved by the U.S. Food and Drug Administration (FDA) for the following indications:1
  - To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)
  - For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for five to 10 days
  - To reduce the risk of recurrence of DVT and PE in patients who have been previously treated
• The FDA-approved doses of PRADAXA are:1
  - 150 mg twice daily for patients with NVAF, DVT, or PE and CrCl >30 mL/min
  - 75 mg twice daily for patients with NVAF and CrCl 15-30 mL/min

HOW DOES PRADAXA WORK?
• PRADAXA is an oral direct thrombin inhibitor (DTI),1 which helps prevent the formation of clots by blocking thrombin, a key component of the clotting process.2
  - The irregular heartbeat associated with NVAF can lead to the formation of blood clots which increase the risk of an ischemic stroke.3
  - Anticoagulant treatment is the standard therapy to treat and prevent blood clots from forming in a vein,4 which may lead to a DVT, or a PE (when the clot travels to the lungs).5
• Unlike with vitamin K antagonists such as warfarin, treatment with PRADAXA does not require regular blood monitoring or related dose adjustments, and has no recommended dietary restrictions.1

WHAT DOES THE CLINICAL RESEARCH SHOW?

**NVAF**
The efficacy and safety of PRADAXA in patients with NVAF were established in the RE-LY® trial,1 one of the largest stroke prevention clinical studies ever conducted with NVAF patients.
• The 18,113-patient RE-LY trial showed that, compared to well-controlled warfarin (N=6,022), PRADAXA 150 mg (N=6,076) significantly reduced the risk of stroke and systemic embolism by 35% (primary efficacy endpoint: 135 [2.2%] vs. 203 [3.4%] events), ischemic stroke by 24% (104 [1.7%] vs. 134 [2.2%] events), and hemorrhagic stroke by 74% (12 [0.2%] vs. 45 [0.8%] events).
• Treatment with PRADAXA 150 mg was associated with a similar rate of major bleeds compared to warfarin (409 events [3.4%] vs. 611 [16.1%]).

**DVT AND PE**
The approval of PRADAXA for DVT and PE was based on results from four global Phase III studies.1
• The RE-COVER® (N=2,539) and RE-COVER II™ (N=2,568) trials, which included patients with DVT and PE who were treated with parenteral anticoagulant therapy for five to 10 days, showed PRADAXA 150 mg (RE-COVER® N=1,274; RECOVER II™ N=1,279) was non-inferior to warfarin (RE-COVER® N=1,265; RECOVER II™ N=1,289) in reducing DVT and PE after a median of 174 days of treatment (RE-COVER® efficacy endpoint: 34 [2.7%] vs. 32 [2.5%] events; RE-COVER II™ primary efficacy endpoint: 34 [2.7%] vs. 30 [2.3%] events), and was associated with lower rates of major bleeding: 101 (4.0%) vs. 170 (6.7%); and any bleeding: 611 (16.1%) vs. 567 (22.7%), but a higher rate of any GI bleeding (3.1% vs. 2.4%).

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Please see Important Safety Information on pages 3 and 4.
Please see full Prescribing Information, including boxed WARNING and Medication Guide.
426 [3.6%]), a lower rate of intracranial hemorrhage (39 [0.3%] vs. 91 [0.8%]), and showed numerically lower rates of fatal and life-threatening bleeds (30 [0.3%] vs. 42 [0.4%] and 183 [1.5%] vs. 221 [1.9%], respectively).

- There was a higher rate of major gastrointestinal (GI) bleeds in patients receiving PRADAXA 150 mg than in patients receiving warfarin (1.6% vs. 1.1%), and a higher rate of any GI bleeds (5.7% vs. 3.9%, respectively).

- The rate of all-cause mortality was lower with PRADAXA 150 mg than with warfarin (3.6% per year vs. 4.1% per year). The rate of vascular death was lower on PRADAXA 150 mg compared to warfarin (2.3% per year vs. 2.7% per year). Non-vascular death rates were similar in the treatment arms.

- In RE-LY, a higher rate of clinical myocardial infarction was reported in patients who received PRADAXA (0.7 per 100 patient-years for 150 mg dose) than in those who received warfarin (0.6).

PRADAXA 150 mg twice daily is the only medication among the newer oral anticoagulants (NOACs) to demonstrate superior reduction of ischemic stroke compared to warfarin in patients with NVAF. PRADAXA also demonstrated a similar rate of major bleeding events.¹

The 2,856-patient RE-MEDY™ trial, which included patients who had been previously treated for an acute DVT and PE with anticoagulant therapy for three to 12 months, showed PRADAXA 150 mg (N=1,430) was non-inferior to warfarin (N=1,426) in reducing DVT and PE after a median of 534 days of treatment (primary efficacy endpoint: 26 [1.8%] vs. 18 [1.3%] events), and was associated with lower rates of major bleeding: 13 (0.9%) vs. 25 (1.8%); clinically relevant non-major bleeding: 71 (5.0%) vs. 125 (8.8%); and any bleeding: 278 (19.4%) vs. 373 (26.2%), but a higher rate of any GI bleeding (3.1% vs. 2.2%).

The 1,343-patient RE-SONATE® trial, which included patients who had been previously treated for an acute DVT and PE with anticoagulant therapy for six to 18 months, showed PRADAXA 150 mg (N=681) reduced the risk of DVT and PE recurrence by 92% compared to placebo (N=662) after a median of 182 days of treatment (primary efficacy endpoint: 3 [0.4%] vs. 37 [5.6%] events). PRADAXA was associated with higher rates of major bleeding: 2 (0.3%) vs. 0; any bleeding: 72 (10.5%) vs. 40 (6.1%); clinically relevant non-major bleeding: 34 (5.0%) vs. 13 (2.0%); and any GI bleeding (0.7% vs. 0.3%).

In the active-controlled VTE studies, a higher rate of clinical myocardial infarction was reported in patients who received PRADAXA 150 mg (20 [0.66 per 100 patient-years]) than in those who received warfarin (5 [0.17 per 100 patient-years]). In the placebo-controlled study, a similar rate of non-fatal and fatal clinical myocardial infarction was reported in patients who received PRADAXA 150 mg (1 [0.32 per 100 patient-years]) and in those who received placebo (1 [0.34 per 100 patient-years]).

In the four pivotal studies, patients on PRADAXA 150 mg had a similar incidence of GI adverse reactions (24.7% vs. 22.7% on warfarin). Dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) occurred in patients on PRADAXA 150 mg in 7.5% vs. 5.5% on warfarin, and gastritis-like symptoms (including gastritis, GERD, esophagitis, erosive gastritis and gastric hemorrhage) occurred at 3.0% vs. 1.7%, respectively.
IMPORTANT SAFETY INFORMATION ABOUT PRADAXA

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

(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. If anticoagulation with PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(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. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:
- use of indwelling epidural catheters
- concomitant use of other drugs that affect hemostasis, such as non-steroidal anti inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- a history of traumatic or repeated epidural or spinal punctures
- a history of spinal deformity or spinal surgery
- optimal timing between the administration of PRADAXA and neuraxial procedures is not known

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients who are or will be anticoagulated.

CONTRAINdications
PRADAXA is contraindicated in patients with:
- active pathological bleeding;
- known serious hypersensitivity reaction (e.g., anaphylactic reaction or anaphylactic shock) to PRADAXA;
- mechanical prosthetic heart valve

WARNINGS & PRECAUTIONS
Increased Risk of Stroke with Discontinuation of PRADAXA
Premature discontinuation of any oral anticoagulant, including PRADAXA, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. If PRADAXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

Risk of Bleeding
- PRADAXA increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension). Discontinue PRADAXA in patients with active pathological bleeding.
- Risk factors for bleeding include concomitant use of medications that increase the risk of bleeding (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs). PRADAXA’s anticoagulant activity and half-life are increased in patients with renal impairment.
- Reversal of Anticoagulant Effect: A specific reversal agent for dabigatran is not available. Hemodialysis can remove dabigatran; however clinical experience for hemodialysis as a treatment for bleeding is limited. Activated prothrombin complex concentrates, recombinant Factor VIIa, or concentrates of factors II, IX or X may be considered but their use has not been evaluated. Protamine sulfate and vitamin K are not expected to affect dabigatran anticoagulant activity. Consider administration of platelet concentrates where thrombocytopenia is present or long-acting antiplatelet drugs have been used.

Spinal/Epidural Anesthesia or Puncture
When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulants are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis. To reduce potential risk of bleeding with concurrent use of dabigatran and epidural or spinal anesthesia/analgesia or spinal puncture, consider the pharmacokinetic profile of dabigatran. Placement/removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of dabigatran is low but exact timing to reach a sufficiently low anticoagulant effect in each patient is unknown. If anticoagulation is administered with epidural or spinal anesthesia/analgesia or lumbar puncture, monitor frequently for signs/symptoms of neurological impairment, i.e., midline...
back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), bowel and/or bladder dysfunction. Instruct patients to immediately report if they experience any of the above signs/symptoms. If spinal hematoma is suspected, initiate urgent diagnosis and treatment; consider spinal cord decompression even though it may not prevent or reverse neurological sequelae.

**Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves**
The safety and efficacy of PRADAXA in patients with bileaflet mechanical prosthetic heart valves (recently implanted or implanted more than 3 months prior to enrollment) was evaluated in the phase 2 RE-ALIGN trial. RE-ALIGN was terminated early because of significantly more thromboembolic events (valve thrombosis, stroke, transient ischemic attack, and myocardial infarction) and an excess of major bleeding (predominantly post-operative pericardial effusions requiring intervention for hemodynamic compromise) for PRADAXA vs warfarin. Therefore, the use of PRADAXA is contraindicated in patients with mechanical prosthetic valves. Use of PRADAXA for the prophylaxis of thromboembolic events in patients with AFib in the setting of other forms of valvular heart disease, including bioprosthetic heart valve, has not been studied and is not recommended.

**Effect of P-gp Inducers & Inhibitors on Dabigatran Exposure**
Concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided. P-gp inhibition and impaired renal function are major independent factors in increased exposure to dabigatran. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to increase exposure of dabigatran compared to either factor alone.

**Reduction of Risk of Stroke/Systemic Embolism in NVAF**
- For patients with moderate renal impairment (CrCl 30-50 mL/min), consider reducing the dose of PRADAXA to 75 mg twice daily when dronedarone or systemic ketoconazole is coadministered with PRADAXA.
- For patients with severe renal impairment (CrCl 15-30 mL/min), avoid concomitant use of PRADAXA and P-gp inhibitors.

**Treatment and Reduction in the Risk of Recurrence of DVT/PE**
- For patients with CrCl <50 mL/min, avoid use of PRADAXA and concomitant P-gp inhibitors.

**ADVERSE REACTIONS**
The most serious adverse reactions reported with PRADAXA were related to bleeding.

**NVAF**
- Most frequent adverse reactions leading to discontinuation of PRADAXA were bleeding & gastrointestinal (GI) events
- PRADAXA 150 mg resulted in higher rates of major and any GI bleeds compared to warfarin.
- In patients ≥75 years of age, the risk of major bleeding may be greater with PRADAXA vs warfarin.
- Patients on PRADAXA 150 mg had an increased incidence of GI adverse reactions. These were commonly dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) and gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, hemorrhagic erosive gastritis, and GI ulcer).

**DVT/PE**
- Rates of any GI bleeds were higher in patients receiving PRADAXA 150 mg vs warfarin and placebo.
- In the active-controlled studies, there was a higher rate of clinical myocardial infarction (MI) in PRADAXA patients [20 (0.66/100 patient-years)] vs warfarin [5 (0.17/100 patient-years)]. In the placebo-controlled study, there was similar rate of non-fatal and fatal clinical MI in PRADAXA patients [1 (0.32/100 patient-years)] vs placebo [1 (0.34/100 patient-years)].
- GI adverse reactions were similar in patients receiving PRADAXA 150 mg vs warfarin. They were commonly dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) and gastritis-like symptoms (including gastritis, GERD, esophagitis, erosive gastritis and gastric hemorrhage).

Drug hypersensitivity reactions were reported in ≤ 0.1% of patients receiving PRADAXA.

**Other Measures Evaluated**
In NVAF patients, a higher rate of clinical MI was reported in patients who received PRADAXA (0.7/100 patient-years for 150 mg dose) than in those who received warfarin (0.6)
About the Boehringer Ingelheim Cares Foundation Patient Assistance Programs

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REFERENCES