

Press Release

FDA Approves Pradaxa,¹ Marking a Major Milestone to Reduce the Risk of Stroke in Patients with Non-Valvular Atrial Fibrillation

Demonstrated to significantly reduce stroke compared to warfarin,¹ Pradaxa is first new oral anticoagulant approved by the FDA in more than 50 years

Ridgefield, CT, October 19, 2010 - The U.S. Food and Drug Administration (FDA) has approved Pradaxa[®] (dabigatran etexilate) capsules to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AFib).¹ PRADAXA, an oral direct thrombin inhibitor² that was discovered and developed by Boehringer Ingelheim, is the first new oral anticoagulant approved in the U.S. in more than 50 years. As demonstrated in the RE-LY[®] trial, PRADAXA 150mg taken twice daily has been shown to significantly reduce stroke and systemic embolism by 35 percent beyond the reduction achieved with warfarin,¹ the current standard of care for patients with non-valvular atrial fibrillation. PRADAXA 150mg taken twice daily significantly reduced both ischemic and hemorrhagic strokes compared to warfarin.¹

The FDA approval of PRADAXA¹ provides a new treatment to reduce the risk of stroke for the increasing number of patients with AFib.³ The safety and efficacy profile of PRADAXA was established based on the results of the 18,113 patient RE-LY[®] trial, the largest stroke prevention trial in AFib patients completed to date.⁴ Treatment with PRADAXA does not require blood monitoring or related dose adjustments and has no recommended dietary restrictions.¹ The FDA also approved PRADAXA 75mg twice daily for the small subset of patients who have severe renal impairment.¹

“For many years, physicians have been searching for new options to reduce the risk of stroke faced by millions of patients with atrial fibrillation. Many of these patients are either not receiving anticoagulation therapy or are taking it sub-optimally, placing them at risk for stroke or major bleeding,” explained Jonathan L. Halperin, M.D., Director of Clinical Cardiology Services at the Mount Sinai Medical Center. “Pradaxa represents an exciting new treatment option for patients with non-valvular atrial fibrillation.”

Warfarin, first approved in the 1950's, has been the standard of care and the only oral anticoagulant available in the U.S. for stroke reduction in patients with AFib. Warfarin is efficacious in reducing the risk of stroke in patients with AFib⁵ when within its narrow therapeutic range. In addition, it has the potential for interactions with many commonly used medications, as well as certain foods.⁶ As a result, patients taking warfarin must maintain a consistent diet⁶ and have their INR monitored and managed through regular blood tests⁶ and dose adjustments.⁶

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“This is a special moment which exemplifies innovation in modern medicine. We are thrilled that the FDA’s approval of PRADAXA will bring a novel medicine to patients with non-valvular atrial fibrillation,” said Albert Ros, president and CEO, Boehringer Ingelheim Pharmaceuticals, Inc. “This approval marks a proud moment in our company’s 125-year history and is a shining example of how Boehringer Ingelheim is dedicated to innovating, developing and providing treatments to improve the lives of patients.”

About Atrial Fibrillation and Stroke

Atrial fibrillation, characterized by an irregular heartbeat,⁷ can cause blood clots to form in the heart that can travel to the brain and cause a stroke.⁷ An estimated 2.3 million Americans are living with Afib,³ and the prevalence is expected to increase to 5.6 million by 2050.³ A large managed care database study showed that non-valvular atrial fibrillation represents approximately 95 percent of all atrial fibrillation cases in the U.S.³ Atrial fibrillation increases the risk of stroke nearly five times⁸ and is associated with up to 15 percent of all strokes in the U.S.⁸ Strokes associated with AFib can be about twice as likely to be fatal⁹ or severely disabling as non-AFib strokes.¹⁰ Atrial fibrillation imposes a substantial economic burden to the healthcare system,¹¹ specifically the high costs associated with stroke.¹²

About Pradaxa® (dabigatran etexilate) Capsules

Indications and Usage

PRADAXA is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

IMPORTANT SAFETY INFORMATION ABOUT PRADAXA

CONTRAINDICATIONS

PRADAXA is contraindicated in patients with active pathological bleeding and patients with a known serious hypersensitivity reaction (e.g., anaphylactic reaction or anaphylactic shock) to PRADAXA.

WARNINGS AND PRECAUTIONS

Risk of Bleeding

PRADAXA increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding.

Risk factors for bleeding include:

- Medications that increase the risk of bleeding in general (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs).
- Labor and delivery

Promptly evaluate any signs or symptoms of blood loss, such as a drop in hemoglobin and/or hematocrit or hypotension. Discontinue PRADAXA in patients with active pathological bleeding.

Temporary Discontinuation of PRADAXA

Discontinuing PRADAXA for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of stroke. Lapses in therapy should be avoided, and if PRADAXA must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

Effect of P-gp Inducers and Inhibitors on PRADAXA Exposure

The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces dabigatran exposure and should generally be avoided. P-gp inhibitors ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin, do not require dose adjustments. These results should not be extrapolated to other P-gp inhibitors.

ADVERSE REACTIONS

In the pivotal trial comparing PRADAXA to warfarin, the most frequent adverse reactions leading to discontinuation of PRADAXA were bleeding and gastrointestinal events. PRADAXA 150 mg resulted in a higher rate of major gastrointestinal (GI) bleeds and any GI bleeds compared to warfarin. In patients ≥ 75 years of age, the risk of major bleeding may be greater with PRADAXA than with 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, gastritis, and GI ulcer). Drug hypersensitivity reactions were reported in $<0.1\%$ of patients receiving PRADAXA.

Other Measures Evaluated

The risk of myocardial infarction was numerically greater in patients who received PRADAXA 150 mg than in those who received warfarin.

For full PRADAXA prescribing information, please visit www.pradaxa.com or contact Boehringer Ingelheim's Drug Information Unit at 1-800-542-6257.

About RE-LY®

RE-LY® was a global, Phase III, randomized trial⁴ of 18,113 patients⁴ enrolled in 951 centers in 44 countries,¹³ investigating whether dabigatran etexilate (two blinded doses) was as effective as well-controlled warfarin – INR 2.0 - 3.0 – (open label) for stroke prevention.¹³ Patients with non-valvular AFib and at least one other risk factor for stroke (i.e., previous ischemic stroke, transient ischemic attack, or systemic embolism, left ventricular dysfunction, age ≥ 75 years, age ≥ 65 years with either diabetes mellitus, history of coronary artery disease, or hypertension)¹³ were enrolled in the study for two years with a minimum follow-up period of one year.⁴

The RE-LY® trial utilized the established PROBE (prospective, randomized, open-label, blinded endpoint evaluation) clinical trial protocol,⁴ which has been used in the previous trials of anticoagulation for stroke prevention in patients with AFib.⁴ A PROBE design may reflect the differences in the management of warfarin and dabigatran in clinical practice.⁴

The primary endpoint of the trial was incidence of stroke (including hemorrhagic) and systemic embolism.⁴ Safety endpoints included bleeding events (major and minor), intracerebral hemorrhage, other intracranial hemorrhage, elevations in liver transaminases, bilirubin and hepatic dysfunction and other adverse events.⁴

In the RE-LY® trial, all clinical outcomes were adjudicated in a blinded manner to minimize bias in assessment of outcomes for each treatment.⁴

About Boehringer Ingelheim Pharmaceuticals, Inc.

Boehringer Ingelheim Pharmaceuticals, Inc., based in Ridgefield, CT, is the largest U.S. subsidiary of Boehringer Ingelheim Corporation (Ridgefield, CT) and a member of the Boehringer Ingelheim group of companies.

The Boehringer Ingelheim group is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, it operates globally with 142 affiliates in 50 countries and more than 41,500 employees. Since it was founded in 1885, the family-owned company has been committed to researching, developing, manufacturing and marketing novel products of high therapeutic value for human and veterinary medicine.

In 2009, Boehringer Ingelheim posted net sales of US \$17.7 billion (12.7 billion euro) while spending 21% of net sales in its largest business segment, Prescription Medicines, on research and development.

For more information, please visit <http://us.boehringer-ingelheim.com> and follow us on Twitter at <http://twitter.com/boehringerus>.

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¹ Pradaxa Prescribing Information

² Di Nisio M, et al. "Direct Thrombin Inhibitors." *New England Journal of Medicine*. 2005; 353:1028-40.

³ Go, Alan S., and Elaine M. Hylek et al. Prevalence of Diagnosed Atrial Fibrillation in Adults: National Implications for Rhythm Management and Stroke Prevention: the ATRIA Study. *JAMA*. 2002; 285:2370-2375.

⁴ Ezekowitz MD, et al. "Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulation therapy, warfarin, compared with dabigatran." *American Heart Journal*. 2009; 157: 805-810.

⁵ Hart, et al. "Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation." *Annals of Internal Medicine*. 2007; 146:857-867.

⁶ Bristol-Meyers Squibb. Coumadin Package Insert. Available at: http://packageinserts.bms.com/pi/pi_coumadin.pdf. Accessed on: October 1, 2010.

⁷ NHLBI website. "What is AFib?" Available at: http://www.nhlbi.nih.gov/health/dci/Diseases/af/af_what.html. Accessed on: August 2, 2010.

⁸ Wolf P, et al. Atrial Fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991; 22:983-988.

⁹ Lin HJ, et al. "Stroke Prevention in Atrial Fibrillation: The Framingham Study." *Stroke*. 1996; 27:1760-1764.

¹⁰ Dulli D, et al. "Atrial Fibrillation is Associated with Severe Ischemic Stroke." *Neuroepidemiology*. 2003; 22:118-123.

¹¹ Coyne, K.S., et al. "Assessing the Direct Costs of Treating Nonvalvular Atrial Fibrillation in the United States." *Value in Health*. 2006; 9:348-356.

¹² Harley C., et al. Direct Costs And Health Care Utilization Associated With Stroke in the Presence of Atrial Fibrillation in the United States. ASAS Conference, Feb. 2009.

¹³ Connolly SJ, et al. "Dabigatran versus Warfarin in Patients with Atrial Fibrillation." *New England Journal of Medicine*. 2009; 361:1139-1151.