Press Release

Benefits and Safety of Pradaxa® (dabigatran etexilate mesylate) Repeatedly Confirmed

British Medical Journal publishes biased article regarding PRADAXA

Ridgefield, CT, July 23, 2014 – Boehringer Ingelheim (BI) wants to set the record straight following misleading statements that the *British Medical Journal* (BMJ) published today regarding Pradaxa® (dabigatran etexilate mesylate). We are concerned that this publication may alarm patients and prompt them to stop taking PRADAXA, thereby increasing their risk of stroke.

To be clear, many of the allegations made by BMJ were reported months ago in the media and have been previously addressed in full by BI.

Our company has provided regulators with the complete data set and analyses of clinical evidence demonstrating PRADAXA's benefits and safety, and FDA and EMA have affirmed RE-LY®'s conclusions and state that PRADAXA provides an important health benefit when used as directed.

BMJ was provided this information by Boehringer Ingelheim, but chose not to include it.

Contrary to the BMJ's accusation that BI withheld analyses, here are the facts: in 2012, our scientists performed preliminary, exploratory simulations with mathematical models to understand whether dose adjustments based on plasma concentrations might further improve PRADAXA's benefits and safety. Because the simulations did not offer reliable predictions of actual patient outcomes, they were not provided to regulators. However, all of the data that was used for the simulations had already been provided.

It is inappropriate to provide regulators simulations that are unreliable and have limitations. Post-hoc exploratory analyses are commonly performed to generate or test hypotheses and are not structured to direct patient management. Thus, they generally are not shared with regulators and first need to be tested in a clinical trial, as many hypotheses, such as the one discussed here, prove to be incorrect.

"Boehringer Ingelheim made a robust effort to find ways to utilize plasma levels to further improve the risk/benefit profile of PRADAXA and it is irrational to suggest otherwise," said Sabine Luik, M.D., senior vice president, Medicine & Regulatory Affairs, Boehringer Ingelheim Pharmaceuticals, Inc. "The truth is the totality of scientific evidence does not support dosing decisions for PRADAXA based on blood levels. The research shows that individual patient characteristics, such as kidney function and certain medications, are critical factors in contributing to the risk of bleeding."

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We are deeply concerned that the BMJ's biased reports could compromise the health and safety of people who may benefit from PRADAXA to reduce their risk of thrombotic events.

Further, innuendos that we should have done more than one trial are false. The pivotal RE-LY trial was intensively discussed and agreed to with regulatory authorities. RE-LY included more than 18,000 patients in over 40 countries, and is one of the largest trials ever conducted in non-valvular atrial fibrillation patients to assess stroke risk reduction. Post-market data assessments from FDA reinforce the favorable risk/benefit profile shown in RE-LY.

FDA published a perspective on the findings from a Mini-Sentinel study in the *New England Journal of Medicine* in 2013. On May 13, 2014, FDA once again reaffirmed PRADAXA's positive benefit-risk profile when it issued a Drug Safety Communication that included results from a Medicare study comparing new users of PRADAXA and warfarin who had received a diagnosis of atrial fibrillation. ***This included more than 134,000 Medicare patients, who were 65 years or older. The new study found that, among new users of blood-thinning drugs, PRADAXA was associated with a lower risk of clot-related strokes, bleeding in the brain and death compared to warfarin.*** The study also found an increased risk of major gastrointestinal bleeding with use of PRADAXA as compared to warfarin, but unlike in RE-LY, no increased risk of MI compared to warfarin.

BMJ also failed to inform its readers that earlier this month, an FDA director authored an article describing atrial fibrillation (AFib), the important role of anticoagulation and novel oral anticoagulants (NOACs) like PRADAXA, rationale behind why the NOACs were approved without an antidote and how the FDA conducts its post-marketing surveillance on all NOACs. The FDA director specifically stated that PRADAXA provides an important health benefit when used as directed.

As with any anticoagulant, there needs to be a balanced consideration of stroke risk reduction and bleeding risk. Patients should not stop taking their anticoagulant medication without first talking to their health care providers. Discontinuing anticoagulation therapy puts a patient at increased risk of stroke.

About Pradaxa® (dabigatran etexilate mesylate) Capsules

Indications and Usage

Pradaxa® (dabigatran etexilate mesylate) capsules is indicated:

- to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation;
- for the treatment of deep venous thrombosis and pulmonary embolism in patients who have been treated with a parenteral anticoagulant for 5-10 days;
- to reduce the risk of recurrence of deep venous thrombosis and pulmonary embolism in patients who have been previously treated

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.

Thromboembolic and Bleeding Events in Patients with Prosthetic Heart Valves
The use of PRADAXA is contraindicated in patients with mechanical prosthetic valves due to a higher risk for thromboembolic events, especially in the post-operative period, and an excess of major bleeding for PRADAXA vs. warfarin. 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.

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).

Please see full Prescribing Information including **Boxed WARNING**, and Medication Guide.

About the Boehringer Ingelheim Cares Foundation Patient Assistance Programs
For more than 125 years, Boehringer Ingelheim has been focused on improving the lives of patients. In keeping with the company commitment to do the most good for the most people, Boehringer Ingelheim works hard to ensure its medicines are accessible to everyone who needs them, including senior citizens and families on limited incomes. The Boehringer Ingelheim Cares Foundation Patient Assistance Programs (BI-PAP) make Boehringer Ingelheim medicines available free of charge to patients who are without pharmaceutical insurance coverage, and who meet certain household income levels.

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 and more than 47,400 employees. Since it was founded in 1885, the family-owned company has been committed to researching, developing, manufacturing and marketing novel medications of high therapeutic value for human and veterinary medicine.

Social responsibility is a central element of Boehringer Ingelheim's culture. Involvement in social projects, caring for employees and their families, and providing equal opportunities for all employees form the foundation of the global operations. Mutual cooperation and respect, as well

as environmental protection and sustainability are intrinsic factors in all of Boehringer Ingelheim's endeavors.

In 2013, Boehringer Ingelheim achieved net sales of about $18.7 billion (14.1 billion euro). R&D expenditure in the Prescription Medicines business corresponds to 19.5% of its net sales.

For more information please visit www.us.boehringer-ingelheim.com/

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