Up-to-date information regarding Pradaxa®

Status July 2014 - Update

Executive Summary

We stand behind the safety and efficacy of Pradaxa® as confirmed by health authorities worldwide. For many patients, Pradaxa® is a lifesaving medication. At Boehringer Ingelheim, patient health and safety is our top priority. As a company with a deep heritage in, and commitment to, scientific innovation, we pride ourselves on ethical clinical research to produce new medicines that are safe and effective. Boehringer Ingelheim and its employees have always acted in an adequate, legally irreproachable and responsible manner regarding the clinical development and marketing of Pradaxa®.

Pradaxa® prevents strokes that can be debilitating and lead to serious health consequences, and that can in the worst case also be fatal. Based on the RE-LY® trial and the number of prescriptions, we estimate that medication has prevented over 130,000 strokes in comparison to no treatment in patients with atrial fibrillation since its market entry.

In its pivotal RE-LY® trial, Pradaxa® showed a superior benefit-risk profile compared to warfarin. Pradaxa® 150 mg twice daily reduced the risk for ischemic and haemorrhagic stroke better than warfarin, and demonstrated at the same time a significantly reduced rate of intracranial, life-threatening, and overall bleeding. The rate of major bleeding was comparable to warfarin. In the lower dose (110 mg twice daily), Pradaxa® showed a similar reduction in the risk of ischemic and haemorrhagic stroke compared to warfarin, but significantly reduced the risk of all types of bleeding. The RE-LY® trial was conducted as a PROBE design trial (prospective, randomised, open label trial with blinded endpoint evaluation), and included 18,113 patients.

Pradaxa® is meanwhile approved in over 100 countries. Post-marketing analyses from both the EMA and the U.S. FDA have regularly affirmed the safety profile of Pradaxa®. Both have recognized since approval that, when used as intended, Pradaxa® provides a significant health benefit by reducing the risk of stroke in patients with atrial fibrillation.

On May 13, the FDA once again reaffirmed the positive benefit-risk profile of Pradaxa® when used as directed. In its ongoing review of Pradaxa®, the FDA completed a new and independent study with more than 134,000 patients, who were 65 years or older. The study compares the drug to the blood thinner warfarin. Results: The risk of myocardial infarction was similar for the two drugs. As in RE-LY®, the study found an increased risk of major gastrointestinal bleeding with use of Pradaxa® as compared to

warfarin. But the most important results are 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, than warfarin.

Both the European Commission as well as the U.S. FDA have approved Pradaxa® for the treatment and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients who have been previously treated.

Padaxa® has been in the market for more than 6 years and is approved in over 100 countries. The clinical experience exceeds that of all other novel oral anticoagulants, equating to over 3 million patient-years in all licensed indications worldwide.

Based on all this experience and the regulatory analyses, there are no new findings that raise doubts about the safety profile of Pradaxa®. In no event should patients consider stopping therapy arbitrarily because this would increase their risk of stroke.

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I) Routine coagulation monitoring

Pradaxa® has been approved in over 100 countries without the necessity of routine coagulation monitoring. Our scientists determined, and the FDA concurred, that doctors should not make dosage decisions based on plasma concentration levels.

Analyses and the raw data of the pivotal approval study were given to the FDA and were publicly discussed by independent experts during the U.S. approval process Based on the data, the FDA determined that routine coagulation monitoring is not necessary for Pradaxa®.

Due to its substance properties, Pradaxa® is different than vitamin K antagonists (anticoagulants like e.g. phenprocoumon, acenocoumarol or Warfarin) and does not require repeat individual adjustment of its dose. Unlike Pradaxa®, Vitamin K antagonists (VKA) have numerous interactions with other medications, food and pathophysiological processes (e.g. fever), and can only provide effective protection from stroke when a patient's value is within a specific therapeutic range. This range is only within an INR value of 2.0 to 3.0 for VKA and is very small. Outside of this range, the patient is at a higher risk of suffering either a stroke or a bleeding. Consequently, patients on these medications need to be monitored and their dose needs to be adjusted regularly. This is not the case with Pradaxa®.

For treatment with Pradaxa®, specific patient characteristics like age, renal function, concomitant medication, and previous stroke are at least as important to determine the individual risk of bleeding as plasma level. Therefore, doctors must consider these clinical factors when selecting a patient's appropriate dose.

II) Antidote

The FDA and other health authorities have recognised and confirmed the efficacy and safety profile of Pradaxa® even without an antidote, most recently in a public statement on the FDA website, written by FDA Deputy Director Ellis Unger. Additionally, post-marketing analyses conducted by the FDA have affirmed that the safety profile of Pradaxa® is consistent with what was expected from RE-LY®.

So far, none of the novel oral anticoagulants (NOACs) have an approved specific antidote for the reversal of their anticoagulant effect in case of acute emergency. Even vitamin K does not fulfil this demand for the VKA, since the effect occurs at the earliest after 4-6 hours and it takes about 24 hours to reach its maximum effect. For patients taking anticoagulants, however, there are a number of options available in everyday clinical practice to reverse the anticoagulant effect and treat bleedings in emergency situations or in case of

surgical interventions. For patients taking Pradaxa®, these options are described in the product label and guide books. The options are almost identical for all anticoagulants, including VKA and NOACs. Additionally, Pradaxa® is the only anticoagulant that can be removed from the blood circulation by (hemo)dialysis due to its low plasma protein binding. In most cases, discontinuing treatment is sufficient to manage a bleeding related to Pradaxa® as the half-life of Pradaxa® (12-14 hours) is much shorter than the half-life of VKA and the medication is cleared from the body much quicker.

A paper published in Circulation in September 2013, the journal of the American Heart Association, presented a retrospective meta-analysis across dabigatran patient populations and reported the following:
"The outcome of major bleeding events in patients on dabigatran was better than in those on warfarin, as evidenced by a shorter stay in the intensive care unit and trend towards lower adjusted all-cause mortality at 30 days after major bleeding."

An antidote to neutralise the anticoagulant effect of Pradaxa® is currently under development.

III) Transparency and Scientific Publications

Boehringer Ingelheim was and is fully transparent towards regulatory authorities.

To provide external access to clinical study data, the company has launched an initiative that will make full clinical trial data for Pradaxa® accessible for research purposes.

Data on Pradaxa® and specifically the RE-LY® trial have been extensively published in peer reviewed journals. In the course of these publications, Boehringer Ingelheim never has and never will put commercial considerations over patient safety. Regarding any scientific publication, Boehringer Ingelheim adheres to the Good Publication Practice Guidelines and the ICMJE Guidelines. Authors are in editorial control of the publication's content and accept full responsibility for the publication by approval of the final version prior to submission for publication. Boehringer Ingelheim may suggest revisions prior to submission for publication. It is the sole decision of the author(s) to accept or not accept these suggestions.

IV) Relevant Information included in the Prescribing Information

An integral part of the approval process is the preparation of prescribing information that describes a medicine's benefits and risks. This is fully coordinated with and approved by the regulatory authorities of the

respective countries and is updated in case of new insights. The prescribing information of Pradaxa® includes a specific and detailed description of the efficacy and safety data for the prevention of stroke and systemic embolism as well as a description of side effects, including observed bleeding incidents. The prescribing information also includes a detailed description of the indication, the contraindications, as well as warnings to provide doctors a balanced risk-benefit-assessment. The results of the pivotal approval study are described in detail in the prescribing information. In addition to the prescribing information, Boehringer Ingelheim regularly informs doctors about new data and analyses on scientific platforms and congresses.

V) Litigation in the U.S.

Since 2012, there were a number of product liability lawsuits against Boehringer Ingelheim pending in the United States. The U.S. civil action has a fundamentally different structure than in Germany. The lawsuits in the U.S. raised claims against the company regarding alleged adverse events in patients that have been treated with Pradaxa®.

They were settled with an agreement on May 28th, 2014. The settlement enables Boehringer Ingelheim to focus solely on its mission of improving patients' lives and allows the company to avoid the distraction and uncertainty of lengthy litigation. The settlement was closed at 650 million US Dollar (appr. 470 million €). Right before the settlement, the U.S. Food and Drug Administration (FDA) had reaffirmed the positive benefit-risk profile of Pradaxa®, when it published the results of a Medicare study of more than 134,000 patients

VI) RE-LY® trial and targeted review

The RE-LY® trial was conducted and coordinated by the independent research institute PHRI that independently managed the database and performed the primary data analyses. Regulatory agencies from around the world reviewed the study's design, protocol, and findings, which were published in *The New England Journal of Medicine*.

During the U.S. litigation proceedings, Boehringer Ingelheim learned that there might be previously uncategorized major bleeding events in the RE-LY® trial. There was one case of a patient who suffered a ruptured spleen due to a car accident, later died, and whose case was counted as a death but was not counted as a major bleed. The plaintiffs' lawyers then suggested that there might be additional, similarly uncounted major bleeding events.

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Our company took these allegations seriously and conducted a targeted review to determine whether there were any other previously unidentified events and how they were distributed among the patients taking dabigatran and warfarin.

RE-LY® was a "mega-trial" involving over 18,000 patients around the world. One of the strengths of RE-LY® being such a sizeable trial is that since the participant numbers are so large, the overall study results regarding bleeding would have changed only if there were a large number of additional unidentified major bleeds in the Pradaxa® arms and not in the warfarin arm. This was not the case.

We conducted the targeted review and then provided documentation to PHRI. The independent experts independently evaluated and categorized the events based on the definitions used in the RE-LY® trial, determining whether the cases presented events that RE-LY® had not yet counted.

While there are additional events that RE-LY® needs to account for, RE-LY®'s conclusions remain unchanged. The additional events were nearly evenly distributed across treatment groups, including warfarin and did not change the study's conclusions on major bleeds, life-threatening bleeds, fatal bleeds, or stroke.