DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22512/S-009

SUPPLEMENT APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Michelle Kliewer,
Director, Drug Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Kliewer:

Please refer to your Supplemental New Drug Application (sNDA) dated October 25 2011, received October 26 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pradaxa (dabigatran etexilate mesylate) 75 and 150 mg Capsules

We acknowledge receipt of your amendments dated November 3 and 18, 2011, and January 9, 2012.

This Changes Being Effected supplemental new drug application provides for the following changes:

- A recommendation to assess renal function prior to and periodically during therapy as clinically indicated and adjust dose accordingly. Please see **DOSAGE AND ADMINISTRATION**, subsection 2.2.

- A recommendation to discontinue Pradaxa in patients who develop acute renal failure and consider alternative therapy. Please see **DOSAGE AND ADMINISTRATION**, subsection 2.2.

- Information about the use of aPTT (and ECT) to assess anticoagulant activity was moved to **DOSAGE AND ADMINISTRATION**, subsection 2.2.

- The **WARNING AND PRECAUTION** subsection, 5.1 Risk of Bleeding, was amended to include:

  - "Pradaxa's anticoagulant activity and half-life are increased in patients with renal impairment."
  - Lack of a specific reversal agent; futility of using vitamin K to affect anticoagulant effect.

- The **WARNING AND PRECAUTION** subsection 5.2, Temporary Discontinuation of PRADAXA, was amended from:

  "Discontinuing anticoagulants, including 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 anticoagulation with PRADAXA must be temporarily discontinued for any reason, therapy should be restarted as soon as possible."

To the following

"Discontinuing anticoagulants, including PRADAXA, for active bleeding, elective surgery, or invasive procedures, places patients at an increased risk of stroke. Minimize lapses in therapy."

- In the **WARNING AND PRECAUTION** subsection, 5.3 Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure, the following changes were made to the third paragraph:

"Consider reducing the dose of PRADAXA to 75 mg twice daily when dronedarone or systemic ketoconazole is coadministered with PRADAXA in patients with moderate renal impairment (CrCl30-50 ml/min). The use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) should be avoided *[see Drug Interactions (7) and Use in Specific Populations (8.6)]*."

To

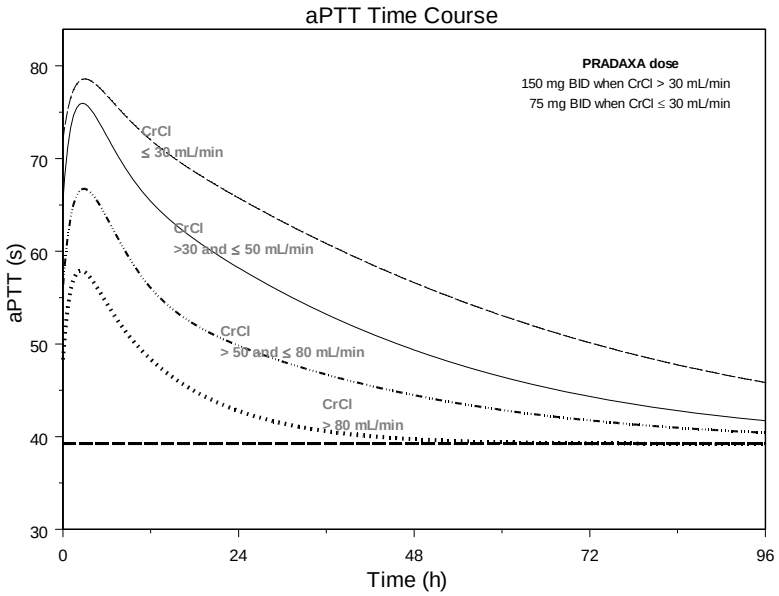
"Consider reducing the dose of PRADAXA to 75 mg twice daily when dronedarone or systemic ketoconazole is coadministered with PRADAXA in patients with moderate renal impairment (CrCl 30-50 mL/min). Avoid use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) *[see Drug Interactions (7) and Use in Specific Populations (8.6)]*."

- Subsection 12.2, **Pharmacodynamics**, of **CLINICAL PHARMACOLOGY,** was extensively amended to read:

"At recommended therapeutic doses, dabigatran etexilate prolongs the coagulation markers such as aPTT, ECT, and TT. INR is relatively insensitive to the exposure to dabigatran and cannot be interpreted the same way as used for warfarin monitoring.

The aPTT test provides an approximation of PRADAXA's anticoagulant effect. The average time course for effects on aPTT, following approved dosing regimens in patients with various degrees of renal impairment is shown in Figure 1. The curves represent mean levels without confidence intervals; variations should be expected when measuring aPTT. While advice cannot be provided on the level of recovery of aPTT needed in any particular clinical setting, the curves can be used to estimate the time to get to a particular level of recovery, even when the time since the last dose of PRADAXA is not precisely known. In the RE-LY trial, the median (10^{th} to 90^{th} percentile) trough aPTT in patients receiving the 150 mg dose was 52 (40 to 76) seconds.

Figure 1 Average Time Course for Effects of Dabigatran on aPTT, Following Approved PRADAXA Dosing Regimens in Patients with Various Degrees of Renal Impairment*



*Simulations based on PK data from a study in subjects with renal impairment and PK/aPTT relationships derived from the RE-LY study; aPTT prolongation in RE-LY was measured centrally in citrate plasma using PTT Reagent Roche Diagnostics GmbH, Mannheim, Germany. There may be quantitative differences between various established methods for aPTT assessment.

The degree of anticoagulant activity can also be assessed by the ecarin clotting time (ECT). This test is a more specific measure of the effect of dabigatran than activated partial thromboplastin time (aPTT). In the RE-LY trial, the median (10^{th} to 90^{th} percentile) trough ECT in patients receiving the 150 mg dose was 63 (44 to 103) seconds.

Cardiac Electrophysiology
No prolongation of the QTc interval was observed with dabigatran etexilate at doses up to 600 mg."

- Lastly, under the subsection of the Medication Guide entitled, "**How should I take PRADAXA?**", the following bullet was added:

> "Call your healthcare provider right away if you fall or injure yourself, especially if you hit your head. Your healthcare provider may need to check you?"

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your January 9, 2012, submission includes final printed labeling (FPL) for your package insert and Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

POSTMARKETING REQUIREMENTS UNDER 505(o)

We remind you of the following postmarketing requirement detailed in the PMR notification letter dated February 8, 2011:

1697-3 Relative bioavailability of a single dose of 150 mg dabigatran etexilate (capsule) when administered alone or in combination with a single dose of 400 mg dronedarone (tablet) or in combination with 400 mg bid dronedarone (tablet) at steady state in healthy male and female volunteers (an open label, randomized, four-sequence, two period cross-over, Phase I study)

The timetable you submitted on February 3, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2011
Trial Completion:	May 2011
Final Report Submission:	October 2011

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the

proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Medication Guide

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY R SOUTHWORTH
01/17/2012