DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22512/S-014

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 May 2, 2012, received May 2, 2012, 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 also acknowledge receipt of your amendments dated June 7 and October 12 and 31, 2012.

This Prior Approval supplemental new drug application provides for a warning for use in patients with prosthetic heart valves, additional information related to overdose, and data regarding the drug interaction with dronederone.

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. These changes are as follows:

FULL PRESCRIBING INFORMATION (FPI) CHANGES

- In Section 5, **WARNINGS AND PRECAUTIONS**, subsection 5.1 **Risk of Bleeding**, the following changes were made:

  - The following sentence was added to 5.1, **Risk of Bleeding**:

    "Hemodialysis can remove dabigatran; however the clinical experience supporting the use of hemodialysis as a treatment for bleeding is limited *[see Overdosage (10)]*."

  - A new warning was added to Section 5:

    "5.4 Patients with Prosthetic Heart Valves
    The safety and efficacy of PRADAXA has not been studied in patients with prosthetic heart valves. Therefore, use of PRADAXA is not recommended in these patients."

- A new subsection, 6.2 **Postmarketing Experience**, was added to section 6, **ADVERSE EVENTS**:

  "6.2 Postmarketing Experience
  The following adverse reactions have been identified during postapproval use of PRADAXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reaction has been identified during postapproval use of PRADAXA: angioedema."

- Section 10, **OVERDOSE** was changed from:

  "Accidental overdose may lead to hemorrhagic complications. There is no reversal agent for dabigatran. In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment with PRADAXA, and investigate the source of bleeding. Dabigatran is primarily excreted in the urine and shows low plasma protein binding. Therefore, dabigatran can be dialyzed with the removal of about 60% of drug over 2 to 3 hours; however, data supporting this approach are limited. Measurement of aPTT or ECT may help guide therapy *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)]."*

  To

  "Accidental overdose may lead to hemorrhagic complications. There is no reversal agent for dabigatran. In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment with PRADAXA, and investigate the source of bleeding. Dabigatran is primarily eliminated by the kidneys with a low plasma protein binding of approximately 35%. Hemodialysis can remove dabigatran; however, data supporting this approach are limited. Using a high-flux dialyzer, blood flow rate of 200 mL/min, and dialysate flow rate of 700 mL/min, approximately 49% of total dabigatran can be cleared from plasma over 4 hours. At the same dialysate flow rate, approximately 57% can be cleared using a dialyzer blood flow rate of 300 mL/min, with no appreciable increase in clearance observed at higher blood flow rates. Upon cessation of hemodialysis, a redistribution effect of approximately 7% to 15% is seen. The effect of dialysis on dabigatran's plasma concentration would be expected to vary based on patient specific characteristics. Measurement of aPTT or ECT may help guide therapy *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)]."*

- In Section 12, **CLINICAL PHARMACOLOGY**, subsection 12.3 **Pharmacokinetics** – *P-gp Inhibitors*, the *Dronederone* section was changed from:

  "Dronedarone: Exposure to dabigatran is 73-99% higher when it is administered with dronedarone than when it is administered alone."

  To

  "Dronedarone: Simultaneous administration of dabigatran etexilate and dronedarone (administered once or twice daily) increases exposure to dabigatran by 70 to 140% compared to dabigatran alone. The increase in exposure is only 30 to 60% higher compared to dabigatran alone when dronedarone is administered 2 hours after dabigatran etexilate."

- In Section 17, **PATIENT COUNSELING INFORMATION**, the following subsection was added:

  "17.6 Prosthetic Heart Valves
  Instruct patients to inform their health care provider if they will have or have had surgery to place a prosthetic heart valve."

- The above changes to the FPI are also reflected in the **HIGHLIGHTS**.

- Other minor and editorial changes were made throughout the label.

MEDICATION GUIDE CHANGES

- The following language was added to the "**What is PRADAXA?"** section:

  "Pradaxa is not for use in people with artificial (prosthetic) heart valves."

- **Lastly, in the "Before you take PRADAXA, tell your doctor if you:"** section, the following was added:

  "have ever had or plan to have a valve in your heart replaced"

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).

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.

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

ENCLOSURE:
Content of Labeling

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
11/02/2012