DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22512/S-007

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 June 8, 2011, received June 8, 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 July 14, August 29, September 23, and October 13 and 28, 2011.

This Prior Approval supplemental new drug application provides for (1) adjustments to dosing when used with concomitant P-gp inhibitors or in patients with renal impairment, and (2) extension of the expiration date to 4 months for opened containers.

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 and with the minor revisions listed below in addition to various minor formatting changes.

- In **HIGHLIGHTS**, under **RECENT MAJOR CHANGES**, a change to the Dosage and Administration section was noted, citing the subsection in parentheses instead of noting the name of the subsection in its entirety in the highlights.
- Also under **RECENT MAJOR CHANGES**, the changes to "**Warnings and Precautions (5.3)**" was cited per 21 CFR 201.57(5).

The following changes were made as part of this labeling supplement:

1. In **DOSAGE AND ADMINISTRATION**, subsection 2.1 (**Recommended Dosage**), the following text was added:

   In patients with moderate renal impairment (CrCl 30-50 mL/min), concomitant use of the P-gp inhibitor dronedarone or systemic ketoconazole can be expected to produce dabigatran exposure similar to that observed in severe renal impairment. Consider reducing the dose of PRADAXA to 75 mg twice daily *[see Drug Interactions (7), Clinical Pharmacology 12)]*.

2. Under subsection 5.3 (**Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure**), of **WARNINGS AND PRECAUTIONS**, the following changes were made. The below was deleted:

> 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 *[see Clinical Pharmacology (12.3)]*.

And replaced with the following language:

> P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran [*see Clinical Pharmacology (12.3)*]. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.
>
> 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). 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)]*.

3. In Section 7, **DRUG INTERACTIONS**, the following statement was deleted:

> 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 *[see Clinical Pharmacology (12.3)]*.

And the following paragraphs were added in its place:

> P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran *[see Clinical Pharmacology (12.3)]*. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.
>
> In patients with moderate renal impairment (CrCl 30-50 mL/min), consider reducing the dose of PRADAXA to 75 mg twice daily when administered concomitantly with the P-gp inhibitor dronedarone or systemic ketoconazole. The use of P-gp inhibitors (verapamil, amiodarone, quinidine, and clarithromycin) does not require a dose adjustment of PRADAXA. These results should not be extrapolated to other P-gp inhibitors *[see Warnings and Precautions (5.3), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.
>
> The concomitant use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCL15-30 mL/min) should be avoided *[see Warnings and Precautions (5.3), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

4. In Section 8.6, **USE IN SPECIFIC POPULATIONS/Renal Impairment**, the following changes were made:

   a. A cross-reference in the first sentence to "Clinical Pharmacology (12.3)" was added.
   b. The following paragraph was added to the end of the subsection:

Adjust dose appropriately in patients with renal impairment receiving concomitant P-gp inhibitors *[see Warnings and Precautions (5.3), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

5. In Section 12.3, **CLINICAL PHARMACOLOGY/Pharmacokinetics/Renal Impairment**, the sentence:

   Based on pharmacokinetic modeling, estimated exposure to dabigatran increases with severity of renal function impairment (Table 3).

   Was amended to:

   Exposure to dabigatran increases with severity of renal function impairment (Table 3).

6. In Section 12.3, **CLINICAL PHARMACOLOGY/Pharmacokinetics**, Table 3 (including the title), was replaced with the following. Please note the footnote that was added:

Table 3 Impact of Renal Impairment on Dabigatran Pharmacokinetics

Renal Function	CrCl (mL/min)	Increase in AUC	Increase in C_{max}	$t_{1/2}$ (h)
Normal	≥ 80	1x	1x	13
Mild	50 - 80	1.5x	1.1x	15
Moderate	30 - 50	3.2x	1.7x	18
Severe[+]	15 – 30	6.3 x	2.1 x	27

[+]Patients with severe renal impairment were not studied in RE-LY. Dosing recommendation in subjects with severe renal impairment is based on pharmacokinetic modeling *[see Dosage and Administration (2.1), Use in Specific Populations (8.6)]*.

7. In Section 12.3, **CLINICAL PHARMACOLOGY/Pharmacokinetics**/P-gp Inhibitors/*Dronederone*, "(1.7 to 2-fold)" was changed to percentages, "(73%-99%)".

8. Under section 16, **HOW SUPPLIED/STORAGE AND HANDLING**, the 30 day expiration date was amended to "4 months".

9. Under Section 17, **PATIENT COUNSELING INFORMATION**, please change "*See Medication Guide"* to *"See FDA-approved patient labeling (Medication Guide)"*.

10. We requested that Section 17.1, **PATIENT COUNSELING INFORMATION/Instructions for Patients**, read as follows:

17.1 Instructions for Patients

- Tell patients to take PRADAXA exactly as prescribed.
- Remind patients not to discontinue PRADAXA without talking to the health care provider who prescribed it.

- Keep PRADAXA in the original bottle to protect from moisture. Do not put PRADAXA in pill boxes or pill organizers.
- When more than one bottle is dispensed to the patient, instruct them to open only one bottle at a time.
- Instruct patient to remove only one capsule from the opened bottle at the time of use. The bottle should be immediately and tightly closed.
- Advise patients not to chew or break the capsules before swallowing them and not to open the capsules and take the pellets alone.

11. We made the following changes to the **MEDICATION GUIDE:**

    a. Under the section, **"What is the most important information I should know about PRADAXA?/ You may have a higher risk of bleeding if you take PRADAXA and:**" the following sub-bullet was added:

        - have certain kidney problems and also take the medicines dronedarone (Multaq®) or ketoconazole tablets (Nizoral®).

    b. Under "**How should I take PRADAXA**?", the following bolded text after the original bullet number three was added:

        - **PRADAXA comes in a bottle or in a blister package.**
        - **Only open 1 bottle of PRADAXA at a time. Finish your opened bottle of PRADAXA before opening a new bottle.**
        - **After opening a bottle of PRADAXA, use within 4 months. See "How should I store PRADAXA?"**
        - **When it is time for you to take a dose of PRADAXA, only remove your prescribed dose of PRADAXA from your open bottle or blister package.**
        - **Tightly close your bottle of PRADAXA right away after you take your dose**

        In the last bullet from the original Medication Guide, "If you take too much PRADAXA, go to the nearest hospital emergency room or call your doctor or the Poison Control Center right away.", the text "or the Poison Control Center right away" was deleted as there is currently no antidote for PRADAXA and no appropriate clinical support.

    c. Under "**How should I store PRADAXA**?", the "30 day" expiration date was amended to "4-months" per recently completed stability testing.
    d. the second bullet was replaced with the following two bolded bullets:

    - **Keep PRADAXA in the original bottle or blister package to keep it dry (protect the capsules from moisture). Do not put PRADAXA in pill boxes or pill organizers.**
        - **Tightly close your bottle of PRADAXA right away after you take your dose.**

12. Finally, the **HIGHLIGHTS** were revised to match the content of the Full Prescribing Information.

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 via 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 with the revisions indicated above 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).

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your October 13, 2011, submission containing final printed carton and container labels.

POSTMARKETING REQUIREMENTS UNDER 505(o)

We remind you of the following postmarketing requirements detailed in the October 19, 2011 approval letter and the PMR notification letter dated February 8, 2011:

1697-1 An *in vitro* study profiling of dabigatran as a substrate or inhibitor of a panel of drug Solute Carrier (SLC) transporters (OATPs, OATs, and OCTs) that are proposed as being relevant by the recently published ITC white paper (Giacomini M, Huang S-M, Tweedie D, et al. Membrane transporters in drug development. *Nature Review Drug Discovery*, 2010, 9: 215-236.)

The timetable you agreed to in your email on October 15, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	December 2010
Study Completion:	November 2011
Final Report Submission:	February 2012

1697-2 An *in vitro* study of the effects of amiodarone and dronedarone on active transport of dabigatran.

The timetable you agreed to in your email on October 15, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	December 2011
Study Completion:	September 2012
Final Report Submission:	December 2012

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

Submit the protocol to your IND 65813, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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
Division of Drug Marketing, Advertising, and Communications
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 Division of Drug Marketing, Advertising, and Communications (DDMAC), 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
Carton and Container Labeling

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

/s/

ALISON L BLAUS
11/09/2011

MARY R SOUTHWORTH
11/09/2011