



NDA 22512/S-017

**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 January 25, 2013, received January 28, 2013, submitted under section 505(b) 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 January 28 and April 11, 2013.

This Prior Approval supplemental new drug application provides for the addition of a boxed warning and a corresponding warning describing an increase in the risk of stroke upon discontinuation of Pradaxa, the addition of information in Section 14 describing the mortality findings from the Phase 3 trial RE-LY, and an adverse reaction detailed in section 6.2, Postmarketing Experience.

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

- The following boxed warning was added to top of the FPI.

**WARNING: DISCONTINUING PRADAXA IN PATIENTS  
WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF  
STROKE**

**Discontinuing PRADAXA places patients at an increased risk of thrombotic events. If anticoagulation with PRADAXA must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant [see *Dosage and Administration (2.6) and Warnings and Precautions (5.1)*].**

- To **WARNINGS AND PRECAUTIONS**, the following changes were made:

The following warning was added:

### **5.1 Increased Risk of Stroke with Discontinuation of PRADAXA**

Discontinuing PRADAXA in absence of adequate alternative anticoagulation increases the risk of thrombotic events. If PRADAXA must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant [*see Dosage and Administration (2.6)*].

Because of the above addition, the below warning was deleted:

### **5.3 Temporary Discontinuation of PRADAXA**

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 **ADVERSE REACTIONS** subsection, **6.2 Postmarketing Experience**, “thrombocytopenia” was added to the list of reactions identified postapproval.
- In Section 14, **CLINICAL STUDIES**, the following was added under Table 5:

“In the RE-LY trial, the rate of all-cause mortality was lower on dabigatran 150 mg than on warfarin (3.6% per year versus 4.1% per year). The rate of vascular death was lower on dabigatran 150 mg compared to warfarin (2.3% per year versus 2.7% per year). Non-vascular death rates were similar in the treatment arms.”

- The above changes are also reflected in their respective sections of the Highlights.

## MEDICATION GUIDE CHANGES

- Because of the new boxed warning and corresponding warning, under the section, **What is the most important information I should know about PRADAXA?**, the following text was added:
  - People with atrial fibrillation (a type of irregular heartbeat) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. PRADAXA lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking PRADAXA, you may have increased risk of forming a clot in your blood.

**Do not stop taking PRADAXA without talking to the doctor who prescribes it for you. Stopping PRADAXA increases your risk of having a stroke.**

PRADAXA may need to be stopped, if possible, prior to surgery or a medical or dental procedure. Ask the doctor who prescribed PRADAXA for you when you should stop taking it. Your doctor will tell you when you may start taking PRADAXA again after your surgery or procedure. If you have to stop taking PRADAXA, your doctor may prescribe another medicine to help prevent a blood clot from forming.

We note that your April 11, 2013, 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 Effectuated” (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 that includes labeling changes 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).

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

### **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, RAC  
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/  
-----

ALISON L BLAUS  
04/24/2013

MARY R SOUTHWORTH  
04/25/2013