DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22512/S-025

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 17 July 2014, received 17 July 2014, 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 also acknowledge receipt of your amendments dated 25 July and 26 August 2014.

This Prior Approval supplemental new drug application provides for changes to the Adverse Reactions and Clinical Studies sections of the Full Prescribing Information to capture updated endpoint event numbers per the RE-LY Reanalysis Investigations.

APPROVAL & LABELING

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 (changes in red):

- In Section 6, **ADVERSE REACTIONS**, subsection Section 6.1, **Clinical Trials Experience**, the following changes were made:
    - Table 2 (Bleeding Events) was amended as follows:

Table 2 Bleeding Events* (per 100 Patient-Years)

	PRADAXA 150 mg twice daily N (%)	Warfarin N (%)	Hazard Ratio (95% CI**)
Randomized patients	6076	6022	
Patient-years	12,033	11,794	
Intracranial hemorrhage	39~~38~~ (0.3)	91~~90~~ (0.8)	0.4~~2~~1 (0.2~~9~~8, 0.6~~1~~0)
Life-threatening bleed	183~~179~~ (1.5)	221~~218~~ (1.9)	0.8~~1~~0 (0.6~~7~~6, 0.9~~9~~8)
Major bleed	409~~399~~ (3.~~4~~3)	426~~421~~ (3.6)	0.9~~4~~3 (0.8~~2~~1, 1.0~~8~~7)
Any bleed	1997~~1993~~ (16.6)	2169~~2166~~(18.4)	0.91 (0.85, 0.96)

*Patients contributed multiple events and events were counted in multiple categories.
**Confidence interval

- The following paragraph in subsection 6.1 was also amended:

  "There was a higher rate of major gastrointestinal bleeds in patients receiving PRADAXA 150 mg than in patients receiving warfarin (1.6% vs. 1.1%, respectively, with a hazard ratio vs. warfarin of 1.5, 95% CI, 1.2 to 1.9), and a higher rate of any gastrointestinal bleeds (5.7 ~~6.1~~% vs. 3.9 ~~4.0~~%, respectively)."

- In Section 14, **CLINICAL STUDIES**, subsection 14.1 **Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation**, the following changes were made:

  - The following table was amended:

Table 7 First Occurrence of Stroke or Systemic Embolism in the RE-LY Study

	PRADAXA 150 mg twice daily	PRADAXA 110 mg twice daily	Warfarin
Patients randomized	6076	6015	6022
Patients (%) with events	135~~134~~ (2.2%)	183 (3%)	203~~202~~ (3.4%)
Hazard ratio vs. warfarin (95% CI)	0.65 (0.52, 0.81)	0.89~~90~~ (0.7~~3~~4, 1.09~~10~~)	
P-value for superiority	0.0001	0.27~~3~~	
Hazard ratio vs. PRADAXA 110 mg (95% CI)	0.72 (0.58, 0.9~~1~~0)		
P-value for superiority	0.00~~5~~4		

  - Table 7's analogous figure, **Figure 2 Kaplan-Meier Curve Estimate of Time to First Stroke or Systemic Embolism,** was also amended to account for these changes.

- The following changes were made to Table 8:

Table 8
Strokes and Systemic Embolism in the RE-LY Study

	PRADAXA 150 mg twice daily	Warfarin	Hazard ratio vs. warfarin (95% CI)
Patients randomized	6076	6022	
Stroke	123~~122~~	187~~186~~	0.64 (0.51, 0.81)
Ischemic stroke	104~~103~~	134	0.7~~65~~ (0.5~~98~~, 0.9~~87~~)
Hemorrhagic stroke	12	45	0.26 (0.14, 0.49)
Systemic embolism	13	21	0.61 (0.30, 1.21)

- **Figure 3 Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics**, was also amended.

- Other minor editorial changes were made throughout the label.

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), 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 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.

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, PharmD
Safety Deputy Director
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
09/04/2014