DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22512/S-023

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 February 14, 2014, received February 14, 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 acknowledge receipt of your amendment dated April 16, 2014.

This Prior Approval supplemental new drug application provides new information related to the drug interaction of dabigatran and ticagrelor (study 1160.142).

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:

- To Section 7, **DRUG INTERACTIONS**, subsection 7.1, **Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation**, ticagrelor was added to the list of P-gp inhibitors that do not require a dose adjustment.

- To Section 12, **CLINICAL PHARMACOLOGY**, subsection 12.3, **Pharmacokinetics**, the following changes were made:

    - Under the subsection, P-gp Inducers – *Rifampin,* the cross-references were updated to Warnings and Precautions (5.5) and Drug Interactions (7).

    - Under subsection, P-gp Inhibitors, the following section was added:

      Ticagrelor: Administration of ticagrelor modestly increases plasma concentrations of dabigatran with the magnitude of increase dependent on the dose and timing of ticagrelor administration. When dabigatran etexilate 110 mg twice daily was coadministered with 90 mg oral ticagrelor twice daily, the $AUC_{\tau,ss}$ and $C_{max,ss}$ of dabigatran increased by 26% and 29%, respectively. When coadministered with a loading dose of 180 mg ticagrelor, the $AUC_{\tau,ss}$ and $C_{max,ss}$ of dabigatran increased by 49% and 65%, respectively; but when ticagrelor 180 mg was given 2 hours after dabigatran, the $AUC_{\tau,ss}$ and $C_{max,ss}$ of dabigatran

increased by only 27% and 24%, respectively *[see Warnings and Precautions (5.2) and Drug interactions (7.1)]*.

- 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).

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}

Norman Stockbridge, M.D., Ph.D.
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/

NORMAN L STOCKBRIDGE
08/14/2014