DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22512/S-027

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 10 December 2014, received 10 December 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 amendments dated 29 January, 20 March, 4 May, and 3 and 20 August 2015.

This Prior Approval supplemental new drug application proposes changes to labeling which is aimed to harmonize the presentation of safety and efficacy data in the labels for all recently approved non-vitamin K-dependent oral anticoagulants (NOACs). The agreed upon changes are as follows:

1. In Section 6, **ADVERSE REACTIONS**, the presentation of the bleeding events was amended to appear as follows. To eliminate redundancy, some information that once appeared prior to the bleeding table (and in the table) was also deleted:

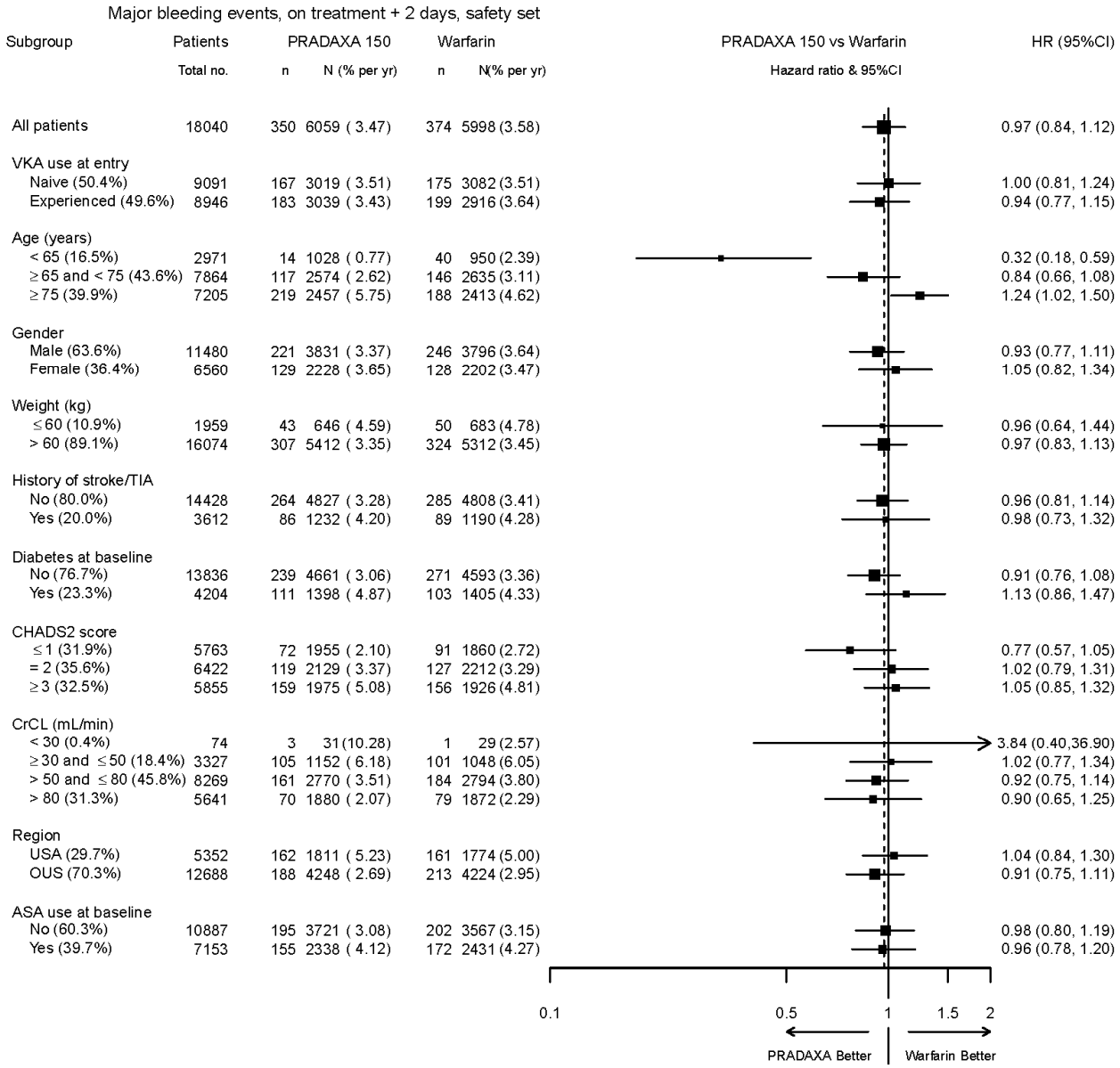
Table 2 Adjudicated Major Bleeding Events in Treated Patients

Event	PRADAXA 150 mg N = 6059 n (%/year)	Warfarin N = 5998 n (%/year)	PRADAXA 150 mg vs. Warfarin HR (95% CI)
Major Bleeding	350 (3.47)	374 (3.58)	0.97 (0.84, 1.12)
Intracranial Hemorrhage (ICH)	23 (0.22)	82 (0.77)	0.29 (0.18, 0.46)
Hemorrhagic Stroke	6 (0.06)	40 (0.37)	0.16 (0.07, 0.37)
Other ICH	17 (0.17)	46 (0.43)	0.38 (0.22, 0.67)
Gastrointestinal	162 (1.59)	111 (1.05)	1.51 (1.19, 1.92)
Fatal Bleeding	7 (0.07)	16 (0.15)	0.45 (0.19, 1.10)
ICH	3 (0.03)	9 (0.08)	0.35 (0.09, 1.28)
Non-intracranial	4 (0.04)	7 (0.07)	0.59 (0.17, 2.02)

[a]Patients during treatment or within 2 days of stopping study treatment. Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories.
[b]Annual event rate per 100 pt-years = 100 * number of subjects with event/subject-years. Subject-years is defined as cumulative number of days from first drug intake to event date, date of last drug intake + 2, death date (whatever occurred first) across all treated subjects divided by 365.25. In case of recurrent events of the same category, the first event was considered.
[c]Defined as bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site or with fatal outcome.
[d]Intracranial bleed included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.
[e]On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14 Clinical Studies.
[f]Fatal bleed: Adjudicated major bleed as defined above with investigator reported fatal outcome and adjudicated death with primary cause from bleeding.
[g]Non-intracranial fatal bleed: Adjudicated major bleed as defined above and adjudicated death with primary cause from bleeding but without symptomatic intracranial bleed based on investigator's clinical assessment.

2. A forest plot was added to Section 6. The population used was On-Treatment plus 2 days:

Figure 1 Adjudicated Major Bleeding by Baseline Characteristics Including Hemorrhagic Stroke Treated Patients



3. The following standard cautionary paragraph was included at the bottom of the forest plot:

> Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

4. In Section 14, **CLINICAL STUDIES**, the forest plot was amended to include the same subgroups as the plot in Section 6 and also to present the data in an identical way as Section 6. The population used to generate the forest plot, however, is different than that in Section 6. The population used in Section 14 was Intent-to-Treat (ITT).

5. In Section 12.3, **CLINICAL PHARMACOLOGY**, Pharmacokinetics, the effect of certain drugs on the pharmacokinetics of a NOAC were depicted in a plot rather than describing the study data in paragraph form. To eliminate redundancy, the descriptions of the studies included in the plot were removed.

6. Other minor editorial changes were also made throughout the label.

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.

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
Senior 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
09/09/2015

MARY R SOUTHWORTH
09/10/2015