DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

NDA: 22512
Supplement: 011
Drug: PRADAXA (dabigatran etexilate mesylate) Capsules
Class: direct thrombin inhibitor
Sponsor: Boehringer Ingelheim
Indication: No change in indication with this supplement
Date of submission: 24 January 2012
Goal date: 24 June 2012

❖ REVIEW TEAM

- Office of New Drugs, Office of Drug Evaluation I, Division of Cardiovascular & Renal Products
  - Team Leader, Medical Reviewer
    - Aliza Thompson, M.D.
  - Regulatory Health Project Manager
    - Alison Blaus

❖ BACKGROUND

Pradaxa (dabigatran etexilate mesylate) is a direct thrombin inhibitor approved for the following:

> PRADAXA is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

In November 2011, the sponsor requested the Division's input on the feasibility of amending the current labeling to more clearly convey the superiority of dabigatran over warfarin. The sponsor explained that such changes would be consistent with the results from the pivotal Phase 3 trial (RE-LY) which clearly demonstrated that Pradaxa 150 mg was superior in reducing strokes relative to warfarin. Furthermore, in light of the Agency's recent approval of rivaroxaban and its approved labeling for the same indication, the sponsor believed that label for Pradaxa should be amended to reflect Pradaxa's distinction.

The Agency met in December of 2011 to review the proposed language and the sponsor's rationale and agreed that the labeling should be amended. The sponsor was asked to submit a formal supplement requesting the changes to Section 14, Clinical Studies. This supplement, S011, is that submission.

❖ REGULATORY TIMELINE

- NDA Approval Date: 19 October 2010
- Sponsor's Initial Superiority Proposal: 16 November 2011
- Supplement 011 Submission Date: 24 January 2012
- Amended Labeling (per S010 Approval) Submitted: 3 May 2012

❖ LABELING NEGOTIATIONS

The agreed-upon changes to Section 14, **CLINICAL STUDIES**, are as follows:

1. The following sentence was edited:

   "At baseline, 40% of patients were on aspirin and 6% were on clopidogrel. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2 to 3) was 64%; the mean percentages of time INR measurements were greater than 4 or less than 1.5 were 2% and 5%, respectively."

   To appear as follows (without the last sentence above):

   "At baseline, 40% of patients were on aspirin and 6% were on clopidogrel. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2 to 3) was 64%."

2. The language related to the superiority of dabigatran over warfarin:

   "The treatment effect was primarily a reduction in stroke. PRADAXA 150 mg twice daily significantly reduced both ischemic and hemorrhagic strokes relative to warfarin."

   Was edited to appear as the following:

   "The treatment effect was primarily a reduction in stroke. PRADAXA 150 mg twice daily was superior in reducing (b) (4) ischemic and hemorrhagic strokes relative to warfarin."

3. The following language and table was deleted from the **CLINICAL STUDIES** section in its entirety:

   "Centers were ranked post hoc by the percentage of time that warfarin-treated patients were in therapeutic range (INR 2 to 3). Findings for stroke/systemic embolism, all-cause mortality, and major bleeds are shown for centers above and below the median level of INR control in Table 6. The benefits of PRADAXA 150 mg relative to warfarin were most apparent in patients enrolled at centers with INR control below the median.

   Table 6 Center INR Control in the RE-LY Study

	Centers with INR control below the median of 67%	**Centers with INR control above the median of 67%**
Stroke/systemic embolism	0.57 (0.42, 0.76)	0.76 (0.55, 1.05)
All-cause mortality	0.78 (0.66, 0.93)	1.01 (0.84, 1.23)
Major bleed	0.82 (0.68, 0.99)	1.08 (0.89, 1.31)

- **REVIEWS**

  Dr. Thompson finalized a clinical review dated 25 May 2012 and recommended that the labeling changes proposed by the sponsor in the 24 January 2012 (detailed above) be approved. Please see Dr. Thompson's review for the rationale for these changes.

- **CONSULTS**

  There were no consults associated with this supplement.

- **CONCLUSION**

  An Approval Letter will be issued for this supplement and signed by Dr. Norman Stockbridge, Division of Cardiovascular & Renal Product's Director.

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
05/29/2012