

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 22-512

Trade Name: PRADAXA

Generic Name: dabigatran etexilate mesylate Capsules

**Sponsor: Boehringer Ingelheim Pharmaceuticals,
Inc.**

Approval Date: 10/19/2010

Indications: to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

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APPLICATION NUMBER:

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APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022512

NDA 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 new drug application (NDA) originally submitted on December 15, 2009 and resubmitted and received on April 19, 2010 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA), for PRADAXA (dabigatran etexilate mesylate) Capsules.

We acknowledge receipt of your amendments dated April 20 (two), 28 and 30, May 3, 4, 5, 6, 7, 10 (two), 13 (three), 14, 17, 21, 24, 26 (two), 27 (four), and 28 (four), and June 1, 7, 17, 18, 22, 23, 25, 29 (two), and 30 (two), July 1 (four), 2, 6 (two), 7 (two), 9 (three), 12 (three), 15 (six), 16, 20, 21 (two), 22 (two), 23, 25 (two), 27 (two), 29 (three), and 30 (two), August 3, 4 (five), 5 (three), 6, 10 (two), 11 (two), 12, 16 (two), 17 (three), 18, 23, and 24 (three), September 3 and 14, October 4, 5, 12, 18 and 19 (three), 2010.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

This new drug application provides for the use of PRADAXA 75 mg and 150 mg capsules, to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. We have approved the 150-mg strength for most patients, and the 75-mg strength for patients with reduced renal function. We are not approving the 110-mg dose, because you have not identified a population in whom there is compelling evidence that the net benefit of the 110-mg dose exceeds that of the 150-mg dose. Moreover, we are concerned that physicians and patients will use the 110-mg dose instead of the 150-mg dose, when the clinical data suggest that the 150-mg dose is superior.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to, the enclosed labeling (text for the package insert, Medication Guide). 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your October 18, 2010, submission containing final printed carton and container labels.

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.

We are waiving the pediatric study requirement for this application because necessary studies are impossible because the disease is rare in children.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks related to the potential for dabigatran etexilate to interact with important drug transporters (Organic Anion Transporting Polypeptides [OATPs], Organic Anion Transporters [OATs], Organic Cationic Transporters [OCTs]), thus causing changes in exposure to other drugs coadministered with dabigatran, and the potential for amiodarone and dronedarone to interfere with the active transport of dabigatran etexilate, which may cause changes in the exposure to dabigatran.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

- 1697-1 An *in vitro* study profiling of dabigatran as a substrate or inhibitor of a panel of drug Solute Carrier (SLC) transporters (OATPs, OATs, and OCTs) that are proposed as being relevant by the recently published ITC white paper (Giacomini M, Huang S-M, Tweedie D, et al. Membrane transporters in drug development. *Nature Review Drug Discovery*, 2010, 9: 215-236.)

The timetable you agreed to in your email on October 15, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	December 2010
Study Completion:	November 2011
Final Report Submission:	February 2012

1697-2 An *in vitro* study of the effects of amiodarone and dronedarone on active transport of dabigatran.

The timetable you agreed to in your email on October 15, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	December 2011
Study Completion:	September 2012
Final Report Submission:	December 2012

Submit the protocol to your IND 65813, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letter dated October 13, 2010.

Your proposed REMS, submitted on December 15, 2009, amended on October 18, 2010 and appended to this letter, is approved. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, an evaluation of patients’ understanding of the serious risks of dabigatran etexilate.

Please see the additional comments regarding the REMS assessment plan in the attachment.

Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post-approval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post-approval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health

Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022512 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 022512
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022512
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please call the Regulatory Project Manager for this application.

If you have any questions, please contact:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Deputy Director
Office of Drug Evaluation-I
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
- Carton and Container Labeling
- REMS
- REMS Assessment Plan Comments

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
10/19/2010