

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
22-512**

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 22512

SUPPL # n/a

HFD # 110

Trade Name PRADAXA

Generic Name dabigatran etexilate

Applicant Name Boehringer Ingelheim

Approval Date, If Known 19 October 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

n/a

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

n/a

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Five

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

n/a

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# n/a n/a

NDA# n/a n/a

NDA# n/a n/a

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# n/a n/a

NDA# n/a n/a

NDA# n/a n/a

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Alison Blaus

Title: Regulatory Health Project Manager

Date: 18 October 2010

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.

Title: Division Director, Division of Cardiovascular & Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

ALISON L BLAUS
10/18/2010

NORMAN L STOCKBRIDGE
10/19/2010



NDA 022512

PRE-APPROVAL REMS NOTIFICATION

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 on April 19, 2010, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA), for dabigatran etexilate capsules.

We also refer to your proposed Risk Evaluation and Mitigation Strategy (REMS) submitted in your application on December 15, 2009, which contained a Medication Guide and communication plan and a timetable for submission of assessments of the REMS.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a 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)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for dabigatran etexilate to ensure the benefits of the drug outweigh the risk of bleeding associated with its use.

We are in the process of reviewing your proposed REMS provided in your NDA submission dated December 15, 2009. However, at this time, based on our current understanding of the risks of dabigatran etexilate, we have determined that a communication plan will not be a necessary element of the REMS.

Therefore, your proposed REMS must only include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that dabigatran etexilate poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of dabigatran etexilate. FDA has determined that dabigatran etexilate is a product for which patient labeling could help prevent serious adverse effects; and that has serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use dabigatran etexilate; and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed dabigatran etexilate.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than 18 months, three years, and seven years after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Before we can continue our evaluation of this NDA, you will need to submit the revised proposed REMS.

For administrative purposes, designate all subsequent submissions related to the proposed REMS “**PROPOSED REMS-AMENDMENT for NDA 022512.**” If you do not submit electronically, please send 5 copies of your REMS-related submissions.

If you have any questions, please contact:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

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

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/s/

ELLIS F UNGER
10/13/2010



NDA 22-512

INFORMATION REQUEST

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 re-submitted on April 19, 2010, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for PRADAXA (dabigatran etexilate mesylate) Capsules.

We have reviewed your amendment dated August 10, 2010 regarding the dissolution specification and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

The data provided in the amendment do not support your proposed dissolution acceptance criterion. The Agency recommends a dissolution acceptance criterion of $Q = \text{(b) (4)}$ in 30 minutes for PRADAXA (dabigatran etexilate mesylate) Capsules. Provide a revised drug product specification that includes dissolution acceptance criterion in accordance with this recommendation. Additionally, revise your stability protocol for your commitment/ annual stability batches to conform to the above dissolution acceptance criterion recommendation.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief,
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22512

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

PRADAXA (DABIGATRAN
ETEXILATE MESYLATE)

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/s/

RAMESH K SOOD
09/01/2010

ONDQA

DATE: July 8 2010

TO: NDA 22-512 (Pradaxa-Dabigatran etexilate mesylate-Capsules, 110 mg and 150 mg capsules) Inspection Team

FROM: Prafull K. Shiromani, Ph.D. 301-796-2133; prafull.shiromani@fda.hhs.gov

THROUGH: Christine Moore, Ph.D.

SUBJECT: Consideration of Inspection (CFI) of Boehringer Ingelheim for NDA 22-512

The purpose of this memo is to identify potential issues for consideration by the Compliance Officer and Field Investigator. This memo includes an overview of the drug product manufacturing process and findings from the CMC review. This NDA submission contained QbD information for development of the drug product.

NDA 22-512 was submitted by Boehringer Ingelheim for PRADAXA[®] (dabigatran etexilate mesylate) 75mg, 110 mg and 150 mg immediate release HPMC capsules, with only the 110 mg and 150 mg potencies intended for the US market. The proposed indication is for the prevention of stroke and systemic embolism and reduction of vascular mortality in patients with atrial fibrillation. The following are the manufacturing sites for the drug product:

- Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach/Riss, Germany (FEI 3002806518), manufacturer of the [REDACTED] (b) (4), testing of excipients and testing of drug product intermediates.
- Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim/Rhein, Germany (FEI 3002806556), all aspects of the manufacturing process of the drug product, testing of excipients, testing of drug product intermediates, primary and secondary packaging of drug product, labeling of drug product, testing of drug product, including stability testing.

Formulation

The formulation consists of the active ingredient [REDACTED] (b) (4)

[REDACTED] Since the drug substance is hydrolytically unstable, especially at low pH in aqueous media, it has to be separated in the formulation from the tartaric acid until ingestion. This is achieved by a [REDACTED] (b) (4)

[REDACTED]

(b) (4)

The manufacturing process follows the following steps:

(b) (4)

The manufacturing process is briefly described in Attachment 1.

The dominant stability indicating characteristic of the drug product is the (b) (4) degradation of the (b) (4), resulting in formation of (b) (4). Other degradation products are known but they are observed in stability studies at low levels.

QbD for Drug Product Development and Manufacture

1a. Identification of Critical Quality Attributes (CQAs) for the drug product: Assay, LOD and Yield have been identified as CQAs by applicant. The yield is a surrogate for the amount of degradation products, i.e. higher the yield lower the content of the degradation products.

1b. Identification of Critical Process Parameters (CPPs): The applicant does not designate any process parameters as critical, however, the following process parameter may be considered to be important based on CMC review of the NDA: (b) (4)

(b) (4)

(b) (4)

(b) (4)

Hence, to achieve sufficient stability of dabigatran etexilate capsules two requirements have to be met:

(b) (4)

Process Parameters and In-Process Controls

The process parameters and in-process controls at critical steps are summarized in Table 1 and the in-process controls established for routine monitoring are summarized in Table 2 in Attachment 2; the rationale of each control is also stated.

Issues for Consideration during Inspection:

From CMC review point of view there are no major quality concerns identified in the application because of the fast dissolution, demonstrated acceptable content uniformity, and stability of this dosage form. However, as part of our commitment to share QbD information across our Offices, the reviewer has identified the following areas in DP manufacturing as primary risks to product quality both at launch and over time.

(b) (4)



(b) (4)



The CMC reviewer is willing to share his knowledge with the investigator. If you have any questions, please email or call the CMC reviewer, Prafull Shiromani Ph.D. – 301-796-2133; Prafull.shiromani@fda.hhs.gov.

7 pages withheld in full immediately after this page as (b)(4) CCI/TS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)

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/s/

DON L HENRY
07/12/2010
on behalf of Prafull Shiromani, PhD

RICHARD T LOSTRITTO
07/15/2010



NDA 22-512

FILING COMMUNICATION

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 on April 19, 2010, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for PRADAXA (dabigatran etexilate mesylate) Capsules.

We also refer to your submissions dated April 20, 28 and 30, May 3, 4, 5, 6, 7, 10, 13, 14, 17, 21, 24, 26, 27, and 28, June 1, 7, 17, 18, 22, 23, 25, 29 and 30, and July 1, 2010.

During our filing review of your application, we identified the following potential review issues and requests for additional information:

1. We are concerned about the quality of follow-up and adherence to protocol for liver function test abnormalities. For example, if the subject was to have a repeat test in one week, it is not clear this was done. If a subject was to have additional viral serology performed, it is not clear if it was performed. We note that some subjects' last values prior to their discontinuation were elevated and abnormal.
2. As part of your Risk Evaluation and Mitigation Strategy (REMS), you explained that you intend to implement a Medication Guide (b) (4) [redacted]. These were not submitted for review. The REMS Supporting Document was also not submitted to the NDA. REMS Supporting Documents should include a thorough explanation of the rationale for how the proposed REMS will mitigate the risks associated with dabigatran use. Please amend the REMS to include the (b) (4) [redacted] and the REMS Supporting Document. Please submit all requested materials to the NDA in WORD format so we may provide comments. Please refer to the Guidance for Industry on the format and content of REMS

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please contact:

Alison Blaus
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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22512

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

PRADAXA (DABIGATRAN
ETEXILATE MESYLATE)

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/s/

NORMAN L STOCKBRIDGE
07/02/2010



NDA 22-512

INFORMATION REQUEST

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 re-submitted on April 19, 2010, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for PRADAXA (dabigatran etexilate mesylate) Capsules.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. Provide further control on the reagent (b) (4) used in the manufacture of drug substance to eliminate this as a potential source of (b) (4) impurities. (e.g., provide a control for the (b) (4) and set appropriate limits in the specification for (b) (4)
2. Provide further control on the reagent (b) (4) used in the manufacture of drug substance to eliminate this as a potential source of (b) (4) impurities. (e.g., provide a control for the (b) (4) and set appropriate limits in the specification for (b) (4)

Drug Product

P.2.3: Manufacturing Process Development:

1. Clarify the role of each of the different forms of tartaric acid, (b) (4), in your manufacturing process for (b) (4)

(b) (4)

statistical method to determine significance [statistical criteria for goodness of fit of model (R^2) and p- and t-values to determine the significance of the regression coefficients (analysis of variance results)].

(b) (4)

(b) (4)

(b) (4)

P.8.2 Postapproval Stability Protocol and Stability Commitment:

14. As per ICH Q1A(R2) 2.2.8-3 place the first three production scale batches on long term stability studies through the proposed shelf life and on accelerated studies for 6 months. All U.S. marketed packages, PP bottle and 6-ct alu/alu blister, should be tested at each time point, as was done with the registration stability batches. The stability protocol used for studies on commitment batches should be the same as for the primary batches. We are interested in potency or package intended for the US market.

Regional Information: A-Labeling and Packaging Insert:

Package Insert-How Supplied:

15. In the 'How Supplied' section the opaque cream-colored section of the capsule is incorrectly stated; it should be 'body' and not (b) (4). Revise appropriate documentation.

Container Label:

16. The statement on the container labels (b) (4) should be reversed to state "Each capsule contains xx mg dabigatran etexilate mesylate equivalent to xx mg dabigatran etexilate".

P.5.1 Specification - Dissolution:

17. Your justification of the dissolution methodology including use of size-adjusted basket for 150 mg tablet is acceptable. However, the Agency recommends a dissolution specification of $Q =$ ^(b)₍₄₎ % in 30 minutes using the following methodology:

- | | |
|----------------|---|
| Apparatus: | USP Apparatus 1 (basket) for 75 ^(b) ₍₄₎ USP Apparatus 1 (basket with adjusted diameter, 24.5 mm) for 150 mg |
| Agitation: | 100 rpm |
| Medium: | 900 mL 0.01M HCl (pH 2.0) |
| Temperature: | 37°C |
| Sampling time: | 30 minutes |
| Determination: | Spectrophotometric at 325 nm. |
- a. Provide all available dissolution data on stability samples at the 30 minute time point; if no such data are available then pull stability samples between 18 and 24 months and provide the 30 minute dissolution data.
- b. Revise your stability protocol for your commitment/annual stability batches so as to conform to the above dissolution recommendation.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Richard Lostritto, Ph.D.
Director,
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application
Type/Number

Submission
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Submitter Name

Product Name

NDA-22512

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

PRADAXA (DABIGATRAN
ETEXILATE MESYLATE)

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/s/

RICHARD T LOSTRITTO
06/29/2010



NDA 022512

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877

ATTENTION: Michelle Kliewer
Director, Drug Regulatory Affairs

Dear Ms. Kliewer:

Please refer to your New Drug Application (NDA) dated April 19, 2010, received April 19, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dabigatran Etexilate Mesylate Capsules, 110 mg and 150 mg.

We also refer to your May 4, 2010, correspondence, received May 4, 2010, requesting review of your proposed proprietary name, Pradaxa. We have completed our review of the proposed proprietary name, Pradaxa and have concluded that it is acceptable.

The proposed proprietary name, Pradaxa, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 4, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Alison Blaus at 301-796-1138.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22512

ORIG-1

BOEHRINGER
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LS INC

PRADAXA (DABIGATRAN
ETEXILATE MESYLATE)

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/s/

CAROL A HOLQUIST
06/14/2010



NDA 22-512

PRIORITY REVIEW DESIGNATION

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 on April 19, 2010, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for PRADAXA (dabigatran etexilate mesylate) Capsules.

We also refer to your submissions dated April 20, 28 and 30, May 3, 4, 5, 6, 7, 10, 13, 14, 17, 21, 24, 26, 27, and 28, and June 1, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is **October 19, 2010**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any post-marketing commitment requests on or before September 21, 2010.

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 indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

Lastly, if while conducting our filing review we identify potential review issues, we will communicate them to you on or before July 2, 2010.

If you have any questions, please contact:

Alison Blaus
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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22512

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

PRADAXA (DABIGATRAN
ETEXILATE MESYLATE)

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/s/

NORMAN L STOCKBRIDGE
06/03/2010



NDA 022512

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Michelle Kliewer
Director, Drug Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. Kliewer:

We have received your new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: PRADAXA (dabigatran etexilate mesylate)

Date of Application: April 19, 2010

Date of Receipt: April 19, 2010

Our Reference Number: NDA 022512

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 18, 2010 in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for

review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, please contact:

Ms. Alison Blaus
Regulatory Health Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22512

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

PRADAXA (DABIGATRAN
ETEXILATE MESYLATE)

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/s/

EDWARD J FROMM
04/27/2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22512

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

PRADAXA (DABIGATRAN
ETEXILATE MESYLATE)

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/s/

ALISON L BLAUS
04/26/2010



NDA 22-512

GENERAL ADVICE

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 December 15, 2009 new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for PRADAXA (dabigatran etexilate mesylate) Capsules.

We also refer to your February 24, 2010 submission containing your plan to rectify problems identified in our Refuse to File letter dated February 12, 2010, as well as issues discussed in our meeting of February 18, 2010. The deficiencies noted pertain to data from your Phase 3 study entitled, "Randomized Evaluation of Long term anticoagulant therapy comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY)."

We have reviewed the above referenced material and have the following comments and recommendations.

1. You plan to perform quality cross checks to assess for underreporting of outcome events. The resulting output will be reviewed by "Tier 1" reviewers who will make a determination for each event as to whether it represents a potential endpoint event. Events that are not designated as potential endpoint events by Tier 1 reviewers will not undergo adjudication.

It is important to put appropriate procedures into place and document how the Tier 1 reviewers arrive at their conclusions. For events assessed by Tier 1 reviewers, the following information should be collected:

- The quality check that triggered the event/finding of concern
- Reviewer's unique identifier
- The conclusion that the Tier 1 reviewer reached regarding the occurrence of a potential endpoint event:
 - i. yes (the potential endpoint event of concern should be specified)
 - ii. no (the rationale for reaching this conclusion should be provided)
 - iii. data are not sufficient to make a determination (the rationale for reaching this conclusion should be provided)

The outputs of the various steps of this process should be documented and submitted to the NDA (including datasets containing the results of the quality cross checks and the determinations of the

Tier 1 reviewers [with reviewer's unique identifier and rationale for reaching the conclusion if the event was not judged to be a potential endpoint event]).

2. Please explain whether or not attempts will be made to obtain additional source documentation (e.g., hospital discharge summaries, records of emergency room visits) for events discovered via your quality cross checks. If you plan to obtain additional source documentation, please describe the decision-making process/algorithm that will be used for determining when and how additional documentation will be pursued.
3. Please clarify the process to be used to generate the submitted lists of adverse event terms that will be used to identify additional endpoint events. Based on our preliminary review, we note that terms that might raise concern for a potential endpoint event were not included (e.g., hemiparesis, lateral medullary syndrome).
4. Although a quality check of CRF 63 was discussed at the February 18, 2010 meeting, we could find no mention of such a quality check in your recent submission. We also requested, but could not find reference to, a quality check of the dates used to censor subjects without an endpoint event (date follow-up information last available for the endpoint event of interest). Please comment.
5. Your submission contained a file titled "event-word-list-clin-input." Please clarify the purpose of this file and explain the significance of its contents.
6. Your submission contained a file titled "description-procedure-words-text-search." Please explain the purpose of this document and the significance of its contents.

Once you have finalized your approach, please submit a document that addresses all of the quality assurance measures that will be taken. This document should include a comprehensive description of all that you plan to submit to the Agency at the end of your quality check, including the names of all datasets amended, and all analyses that might be affected by changes to the data. You should submit new analysis datasets as well as new CRF datasets that have changed. The submission/document should serve as a stand alone reference and be organized in a manner that facilitates review. Please be consistent in your references to any item or quality check between documents within the submission. Ensuring consistency throughout the submission is absolutely critical to the timeliness of our review.

If you have any questions, please contact:

Alison Blaus
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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22512

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

PRADAXA (DABIGATRAN
ETEXILATE MESYLATE)

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/s/

ALISON L BLAUS
03/04/2010

NORMAN L STOCKBRIDGE
03/04/2010

Internal Meeting Minutes

Date: 18 February 2010
Application: NDA 22-512 (IND 65,813)
Drug: dabigatran etexilate
Sponsor: Boehringer Ingelheim (BI)
Meeting Type: Follow-up to Refuse to File

FDA Participants:

** Office of Drug Evaluation I*

Ellis Unger, M.D. Deputy Director

** Division of Cardiovascular & Renal Products*

Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiovascular & Renal Products

Stephen Grant, M.D. Deputy Director

Nhi Beasley, PharmD Medical Reviewer

Aliza Thompson, M.D. Medical Reviewer

Steve Bai, Ph.D. Statistician

Ed Fromm, RPh, RAC Chief Regulatory Project Manager

Alison Blaus Regulatory Project Manager

** Division of Scientific Investigations (DSI)*

Sharon Gershon Reviewer

Boehringer Ingelheim Participants:

Chris Corsico, M.D., MPH US Medicine and Regulatory

Michelle Kliewer US Regulatory

Claudia Lehmann Corporate Biometrics and Data Management (non-US)

Sabine Luik, M.D. Corporate Quality, Regulatory, Pharmacovigilance and Epidemiology (non-US)

Paul Reilly, Ph.D. Team Member Medicine (non-US)

Thor Voigt, M.D. Corporate Medicine (non-US)

Background

Boehringer Ingelheim (BI) has submitted NDA 22-512 to market dabigatran etexilate for the prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation. Dabigatran is being developed by BI for two additional indications; (b) (4)

For demonstration of efficacy and safety, NDA 22-512 relies upon the results from the Phase 3 study entitled, "Randomized Evaluation of Long Term Anticoagulant Therapy Comparing the Efficacy and Safety of Two Blinded Doses of Dabigatran Etexilate with Open Label Warfarin for the Prevention of Stroke and Systemic Embolism in Patients with Non-Valvular Atrial Fibrillation: Prospective, Multi-Centre, Parallel-Group, Non-Inferiority Trial (RE-LY)." An analysis of the data from RE-LY was published in the New England Journal of Medicine, Volume 361 (12); 17 September 2009. Prior to publication in NEJM, the sponsor presented their data to the Division (minutes dated 17 September 2009) and claimed that RE-LY demonstrates the superiority of one dose of dabigatran to warfarin. Because prevention of strokes in patients with non-valvular atrial fibrillation is an important public health concern, the Agency proposed a rolling review. The purpose of a rolling review was to speed the Agency's review of the application but the Agency emphasized that the review would not be less thorough than a standard submission.

The final portion of the NDA was submitted on 15 December 2009. Preliminary review revealed a number of errors in the blood transfusion dataset and the INR dataset. These errors included transcription errors, transposition errors, and auditing errors. Though the Agency recognizes that there will be some errors in the datasets of large trials, the errors found by relatively unsophisticated means in clinically important datasets during preliminary review called into question the overall quality of those datasets. On 12 February 2010, the Agency sent BI a Refuse to File letter. The Agency and BI met on 18 February 2010 to discuss this letter and a plan for resolving the Agency's concerns about the data from RE-LY (proposed "Road Map" submitted on 16 February 2010).

Topics of Discussion

- *Case Report Form (CRF) Audit:* BI agreed to apply additional data quality checks to CRFs 63, 151, and 196. These data quality checks would be described in their updated "Road Map."
- *Identification of Additional Potential Endpoint Events:* The sponsor agreed to provide their algorithm for identifying additional potential endpoint events and reiterated that they will only be adding events and not removing any previously adjudicated outcome events. Dr. Unger stated that BI should also prespecify the time frame (i.e., the number of days over which change occurred) for identifying potential bleeding events based on drops in hemoglobin.
 - *Adjudication:* The sponsor stated that new potential endpoint events identified via the proposed data quality checks would be sent for adjudication. The process for adjudication will mirror that used during the trial (2 blinded adjudicators with a third in the event of non agreement). BI acknowledged that they may not be able to obtain post-operative information or discharge summaries but reported that they will attempt to obtain this information from the sites.
- *Original CRFs:* BI clarified that the original CRFs are retained at the investigator site. When information was recorded on the CRF during the trial, a copy of the CRF was faxed to the academic CRO (PHRI, Hamilton, Canada) responsible for data management. PHRI, therefore, may have more than one faxed copy of any CRF, but not the original. BI has a copy of the last faxed version of each CRF.
- *RE-LY Clinical Trial Monitoring:* Although PHRI was responsible for data management, clinical trial monitoring was performed by BI.
- *Resubmission Contents:* Dr. Stockbridge stated that the following items should be provided in the Complete Response to the Refuse to File Letter:
 - *Revised Study Report* – The document should identify the particular findings that were altered as a result of the data quality checks and should be organized in a manner that facilitates review. The sponsor agreed to provide a hyperlink between the new and previously submitted data/reports (so for example, the revised report should contain the new text, an explanation for the change, and a hyperlink to the previous text/data).
 - *Datasets* –CRF and analysis datasets that were changed as a result of the data quality checks would need to be resubmitted. These new datasets should contain the same variable names and format as the old datasets. A column should be added to the new datasets denoting whether a change was made to a specific data point (Y/N or 0/1). The sponsor was also asked to retain the original dataset names, but to modify the original name by appending the word "new" or some other indicator to distinguish the new datasets from those previously submitted. Datasets that are not altered should not be resubmitted.
 - *Additional Information* – The algorithm for identifying new potential endpoint events, SAS codes for all data quality checks, new analyses, and all datasets used to support the new analyses (if the new analysis datasets were not run off of previously submitted tabulations datasets) should also be submitted in the Complete Response.
- *TimeCens.xpt* – Dr. Bai informed the sponsor that he could not locate the datasets used to create their time to censoring analysis (i.e., timecens.xpt). He asked the sponsor to tell him the location of these datasets. If these datasets were not previously submitted they should be submitted to the NDA.

- **Post Meeting Note:** The sponsor acknowledged that the censoring analysis datasets had not been submitted to the NDA. The datasets were submitted to the NDA on 24 February 2010.

Action Items:

- Boehringer Ingelheim agreed to provide the Agency with an updated “Road Map.” The updated “Road Map” would address the issues raised and requests made at the meeting. The Division agreed to provide the sponsor with written feedback on this updated “Road Map.”

Post Meeting Note:

- The updated “Road Map” was submitted to the Division on 24 February 2010.
- The submission was reviewed and comments were sent to the sponsor (letter dated 1 March 2010)

Minutes preparation: _____
Alison Blaus

Concurrence, Chair: _____
Norman Stockbridge, M.D., Ph.D.

Draft: ab 1Mar10
Final: ab 15Mar10

Reviewed:
Beasley 3/8/10
Thompson 3/9/10
Grant 09 Mar 2010
Unger 3/11/10
Stockbridge 3/13/10

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)
NDA-22512	GI-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)

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/s/

ALISON L BLAUS
03/15/2010

NORMAN L STOCKBRIDGE
03/15/2010



NDA 22-512

REFUSAL TO FILE

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 December 15, 2009 new drug application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for PRADAXA (dabigatran etexilate mesylate) Capsules.

After a preliminary review, we find that your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the reason outlined below.

In support of the proposed indication, you conducted a single phase 3 trial titled “Randomized Evaluation of Long term anticoagulant therapY comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY).” The primary objective of RE-LY was to demonstrate the efficacy and safety of dabigatran etexilate in subjects with non-valvular atrial fibrillation for the prevention of stroke and systemic embolism.

We note that you claim an overall data error rate of 0.1% or less for primary outcome data and 0.25% or less for all other data. However, we found data errors in five out of six subjects in our initial analysis of your INR.xpt data. These errors are described in Tables 1 and 2. These errors include transcription errors, transposition errors, and auditing errors.

Table 1. Subjects checked by reviewer with error in INR.xpt file

USUBJID	Date yyyy-mm-dd	INR.xpt		CRF	
		INR	Dose (mg)	INR	Dose (mg)
1160-0026-00113002	2007-06-21		7		8
1160-0026-01361033	2007-08-13	7.4		2.4	
1160-0026-01361033	2008-08-18	9		3.0	
1160-0026-00003010	2007-09-28	missing	missing	1.6	3
1160-0026-00007006	2007-09-17		83.7		3.7
1160-0026-00007006	2007-09-24		23.7		3.7

Table 2. Transposition errors for subject 1160-0026-01361033

Date	Average daily dose (mg)	INR
23DEC2008	1.5	8.6
30DEC2008	2	9
03FEB2009	2.2	9
10MAR2009	3.5	9

We note that you closed site 6; therefore, we do not comment on problems evident in the data from that site.

We recognize that that there may be occasional inaccuracies in a large trial database; however, the frequency of errors in the data sets impedes our ability to perform an adequate review, and undermines our confidence in your data.

In recognition of the importance of this priority application, we proposed a rolling review. We will, of course, continue our review of parts of your application that are complete and reviewable, such as the chemistry and pharmacology toxicology sections. In addition, the clinical reviewers will work with you to evaluate further data integrity issues and to provide comment on your plans to respond to these issues.

Please note that the above comments are only a partial listing of deficiencies, and that there may be additional deficiencies with your submission that are not included in this letter.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, please contact:

Alison Blaus
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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22512

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

PRADAXA (DABIGATRAN
ETEXILATE MESYLATE)

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/s/

NORMAN L STOCKBRIDGE
02/12/2010

REQUEST FOR CONSULTATION

TO (Office/Division): Raanan Bloom, OPS/PARS, (301)796-2185

FROM (Name, Office/Division, and Phone Number of Requestor):
Don Henry Project Manager, ONDQA, 301-796-4227 on behalf of P. Shiromani

DATE
1/11/2010

IND NO.

NDA NO.
22-512

TYPE OF DOCUMENT
original submission

DATE OF DOCUMENT
September 17, 2009

NAME OF DRUG
DABIGATRAN
ETEXILATE MESYLATE

PRIORITY CONSIDERATION
priority

CLASSIFICATION OF DRUG
cardio-renal

DESIRED COMPLETION DATE
3/30/2010

NAME OF FIRM: BOEHRINGER Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Environmental consult is required to review the ecotoxicity and environmental fate data provided in the applicant's Environmental Assessment Report and determine its acceptability

SIGNATURE OF REQUESTOR
{See appended electronic signature page}

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22512

GI-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

PRADAXA (DABIGATRAN
ETEXILATE MESYLATE)

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/s/

DON L HENRY
01/11/2010

RAMESH K SOOD
01/11/2010



NDA 022512

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Michelle Kliewer
Director, Drug Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. Kliewer:

We have received your new drug application (NDA) submitted section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: PRADAXA (dabigatran etexilate mesylate)

Date of Application: December 15, 2009

Date of Receipt: December 15, 2009

Our Reference Number: NDA 022512

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 13, 2010 in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for

review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, please contact:

Ms. Alison Blaus
Regulatory Health Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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ORIG-1

BOEHRINGER
INGELHEIM
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PRADAXA (DABIGATRAN
ETEXILATE MESYLATE)

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/s/

EDWARD J FROMM
01/05/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE and Nina Ton		FROM: Alison Blaus, ODE 1/DCaRP, (301)796-1138		
DATE 16 December 2009	IND NO. 65-813	NDA NO. 22-512	TYPE OF DOCUMENT NDA Submission	DATE OF DOCUMENT 15 December 2009
NAME OF DRUG PRADAXA (dabigatran etexilate)		PRIORITY CONSIDERATION PRIORITY	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE 15 May 2009
NAME OF FIRM: Boehringer - Ingelheim				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input checked="" type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Hello! This NDA was submitted with a REMS (Communication Plan and Medication Guide). Please review the appropriate documents (link to the REMS below). This was a rolling submission (last piece arriving on 15Dec09 which included the REMS). Labeling can be found in the 8Dec09 submission (link below). I will include DRISK on all filing, team, and labeling meetings as appropriate. Please let me know the DRISK reviewer assigned to this application. Thank you! REMS EDR Location: \\CDSESUB1\EVSPROD\NDA022512\0007 Label EDR Location: \\CDSESUB1\EVSPROD\NDA022512\0010				
SIGNATURE OF REQUESTER: Alison Blaus		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	GI-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)
NDA-22512	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)

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/s/

ALISON L BLAUS
12/16/2009

REQUEST FOR CONSULTATION

TO (Office/Division): **Wayne Amchin, DDMAC, (301) 796-0421**

FROM (Name, Office/Division, and Phone Number of Requestor): **Alison Blaus, ODE 1/DCaRP, (301)796-1138**

DATE 16 December 2009	IND NO. 65,813	NDA NO. 22-512	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT 15 December 2009
NAME OF DRUG PRADAXA (dabigatran etexilate) Tablets		PRIORITY CONSIDERATION PRIORITY	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE 15 April 2009

NAME OF FIRM: **Boehringer - Ingelheim**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILTY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|--|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|--|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the labeling for this NDA (22-512 - dabigatran). I will include you and your team on the filing meeting as well as all team/labeling meetings. This was a rolling submission (last piece received 15 Dec 09), the labeling was submitted on 8Dec09 and is at the below link.

EDR Location: \\CDSESUB1\EVSPROD\NDA022512\0010

SIGNATURE OF REQUESTOR Alison Blaus	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	GI-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)
NDA-22512	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)

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/s/

ALISON L BLAUS
12/16/2009

REQUEST FOR CONSULTATION

TO (Office/Division): Patrick Marroum, Biopharmaceutics,
ONDQA

FROM (Name, Office/Division, and Phone Number of Requestor):
Don Henry Project Manager, ONDQA, 301-796-4227 on
behalf of P. Shiromani/K. Srinivasachar

DATE
12/3/2009

IND NO.

NDA NO.
22-512

TYPE OF DOCUMENT
original submission

DATE OF DOCUMENT
09/30/2009

NAME OF DRUG
Pradaxa (dabigatran)

PRIORITY CONSIDERATION
priority

CLASSIFICATION OF DRUG
cardio-renal

DESIRED COMPLETION DATE
2/28/2010

NAME OF FIRM: Boehringer Ingelheim Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input checked="" type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input checked="" type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: The product is intended for the prevention of stroke and systemic embolism in patients with atrial fibrillation and hence, the NDA has been placed on an accelerated review time-line. It is a rolling submission, with complete submission expected mid-Dec. CMC is contained in the Presubmission 0002 of 9/30/2009. Review of the dissolution method and specification are requested. In addition, you are requested to review the in-vitro data to support the bioequivalence between two drug product manufactured with different (b) (4) of the compound.

The dissolution method is USP Apparatus 1 (basket) for 75mg (b) (4) and USP Apparatus1 (basket (b) (4)) for 150 mg; 100 rpm; 900 mL 0.01M HCl (pH 2.0). Specification: Q = (u) (4) @45 minutes - refer to 3.2.P.5.6. The Drug Substance (Code BIBR 1048 MS) is classified as BCS class 2 (low solubility/high permeability) - refer to 3.2.P.2. For the Drug Product (pellets in capsule): Tartaric acid is included as a (b) (4) tartaric acid (b) (4)

- refer to 3.2.P.2.

SIGNATURE OF REQUESTOR
{ See appended electronic signature page }

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	GI-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)

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/s/

DON L HENRY
12/07/2009

RAMESH K SOOD
12/08/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE		FROM: Alison Blaus, ODE 1/DCaRP, (301)796-1138		
DATE 16 November 2009	IND NO. 65,813	NDA NO. 22-512	TYPE OF DOCUMENT NDA Submission	DATE OF DOCUMENT 13 November 2009
NAME OF DRUG Dabigatran etexilate		PRIORITY CONSIDERATION Priority NDA Review	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 15 March 2010
NAME OF FIRM: Boehringer-Ingelheim				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Carton/Container Labels				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review these carton/container labels for this rolling NDA review of dabigatran. Dabigatran is indicated in patients with atrial fibrillation The review clock will start with the last piece of the submission (approximately arriving on 15 December 2009). EDR Location: \\CDSESUB1\EVSPROD\NDA022512\0008 PDUFA DATE: TBD (approx. 15 June 2010) ATTACHMENTS: Draft Package Insert, Container and Carton Labels (please see these documents at the above EDR location). CC: Archival IND/NDA 22-512 HFD-110/Division File HFD-110/RPM HFD-110/Reviewers and Team Leaders				
NAME AND PHONE NUMBER OF REQUESTER			METHOD OF DELIVERY (Check one)	

Alison Blaus	<input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22512

ORIG-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

PRADAXA (DABIGATRAN
ETEXILATE MESYLATE)

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/s/

ALISON L BLAUS
11/17/2009

REQUEST FOR CONSULTATION

TO (Office/Division): Karl Lin, Team Leader, Division of Biometrics 6 (Applications in Pharmacology / Toxicology)

FROM (Name, Office/Division, and Phone Number of Requestor): Alison Blaus, ODE 1/DCaRP, (301)796-1138

DATE 12 November 2009	IND NO. 65,813 (102,130 ACS)	NDA NO. 22-512	TYPE OF DOCUMENT NDA Submission	DATE OF DOCUMENT 17 September 2009
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NAME OF DRUG dabigatran etexilate	PRIORITY CONSIDERATION Priority NDA	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 11 December 2009
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NAME OF FIRM: Boehringer-Ingelheim

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|---|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|---|

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|---|
| <input type="checkbox"/> CLINICAL | <input checked="" type="checkbox"/> NONCLINICAL |
|-----------------------------------|---|

COMMENTS / SPECIAL INSTRUCTIONS:

We are requesting your assistance in the review of the carcinogenicity data for dabigatran. This submission is located at the following links:

\\CDSesub1\EVSPROD\NDA022512\0000\m4\datasets\boi-287-042668\tabulations\tumor4.xpt

\\CDSesub1\EVSPROD\NDA022512\0000\m4\datasets\boi-288-042959\tabulations\tumour288.xpt

The data regarding carcinogenicity arrived in the submission dated 17Sep09 (module 4.2.3.4.1). The Pharmacology/Toxicology reviewer for this IND/NDA is Patricia Harlow (301-796-1082). Once a statistician has been assigned, please let myself and Pat know that person. This data will need to be taken in front of the Exec CAC in January, so we are hoping to have your review 30day from now (or sooner) since we will need it to finalize our reviews. If you have any questions, please do not hesitate to contact me. Thank you in advance! Alison

SIGNATURE OF REQUESTOR Alison Blas	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22512

GI-1

BOEHRINGER
INGELHEIM
PHARMACEUTICA
LS INC

PRADAXA (DABIGATRAN
ETEXILATE MESYLATE)

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/s/

ALISON L BLAUS
11/12/2009