

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-512

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 22-512, PRADAXA (dabigatran etexilate) Capsules
75 mg and 150 mg
Date: 18-OCT-2010

Introduction

PRADAXA (dabigatran etexilate) Capsules (immediate release) are for the prevention of stroke in atrial fibrillation (thrombin inhibitor). The approved drug product will be supplied in two strengths 75 mg and 150 mg. An originally proposed 110 mg strength is not going to be marketed for clinical reasons. **ONDQA recommends approval of this NDA.**

Administrative

The original submission of this rolling 505(b)(1) NDA was received 15-DEC-2009 from Boehringer Ingelheim Pharmaceuticals, Inc., of Ridgefield, Connecticut. The drug substance is a new molecular entity (NME). The 15-DEC-2009 submission was refused to file (RTF) on 12-FEB-2010 for clinical reasons. However, due to the priority / rolling status of the application, the CMC review remained ongoing after the RTF. The application was resubmitted on 19-APR-2010 and was granted priority review status.

A total of five CMC amendments were reviewed between 28-APR-2010 and 29-JUL-2010. Two team reviews were submitted by ONDQA dated 29-JUN-2010 and 07-SEP-2010.

This NDA is supported by ten DMF's. Consults for (b) (4) (EES acceptable -21-MAY-2010), (b) (4) (dissolution), are EA (acceptable FONSI) acceptable.

ONDQA recommends approval from the Chemistry, Manufacturing and Controls perspective.

Drug Substance (dabigatran etexilate mesylate)

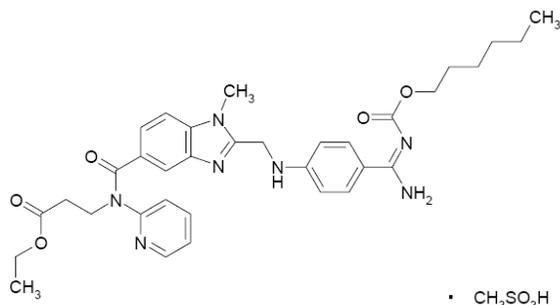
The drug substance is dabigatran etexilate mesylate [IUPAC Name: Ethyl *N*-{[2-({[4-((*E*)-amino {(hexyloxy)carbonyl]imino} methyl)phenyl]amino} methyl)-1-methyl-1*H*-benzimidazol-5-yl]carbonyl}-*N*-pyridin-2-yl-β-alaninate methanesulfonate.

It is a mesylate salt of a base which also contains two ester functional groups (ethyl ester and etexilate ester) . The di-ester is essentially a prodrug for the corresponding zwitterion. However, the nomenclature and strength are based on the relevant di-ester, intrinsic neutral form.

Dabigatran etexilate mesylate drug substance is a yellow-white or yellow crystalline powder. It is manufactured at 4 sites by two manufacturing processes. Two (b) (4) anhydrous polymorphic forms (I and II) and a (b) (4) form have been identified. The drug substance is composed primarily of form I, containing up to (b) (4) form II and in the solid state they cannot be transformed into the (b) (4) form.

Dabigatran etexilate mesylate drug substance is a BCS Class II (low solubility / high permeability). Solubility is pH dependent (higher at pH < 3).

Structural Formula:



Molecular Formula: C₃₄H₄₁N₇O₅ · CH₄O₃S
Molecular Weight (mesylate salt): 723.86 g/mol
Molecular Weight (free base): 627.75 g/mol

The approved drug substance retest interval is (b) (4) months.

Drug Product (immediate release capsules).

The drug product is supplied as immediate release capsules. Strengths corresponding to 75 mg, 110 mg, and 150 mg of dabigatran etexilate were developed. For clinical reasons, the 110 mg strength will not be approved.

The formulation consists of standard compendial ingredients; including tartaric acid which (b) (4) of the drug substance by (b) (4). However the drug substance is also acid sensitive. To circumvent this incompatibility, the tartaric acid (b) (4). The dried pellets are filled into hard gelatin capsules as follows:

75 mg strength in size 2 capsule, as light blue cap and cream colored body imprinted with company logo and R75 in black ink

150 mg strength in size 0 capsule; same color cap and body imprinted with company logo and R150 in black ink.

The filled capsules are packaged in bottles of (60 count with desiccant) and blisters (6 capsules per blister card, 10 blister cards per box). Revised stability specifications include an acceptance criterion of Q (b) (4) / 30 minutes.

The applicant's drug product stability package utilized a complex matrix approach. However, a review finding of adequate was determinable in support of the proposed expiry. Because some stability data are missing in the applicant's matrix approach, the applicant agreed to the following as a **post marketing agreement**:

Boehringer Ingelheim commits to conduct stability studies on three production scale drug product batches per strength up to the proposed shelf life at real time (long term storage conditions) and accelerated storage conditions in the proposed U.S. marketed bottle and blister packages.

The drug product is to be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) A twenty-four (24) month expiry is approved for both strengths in both bottle and blister package presentations. Additional storage and use instructions include:

Bottles: Once opened, the product must be used within 30 days. Keep the bottle tightly closed. Store in the original package to protect from moisture.

Blisters: Store in the original package to protect from moisture.

ONDQA recommends approval of this NDA from the CMC perspective.

Rik Lostritto, Director, ONDQA Division I

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

/s/

RICHARD T LOSTRITTO
10/19/2010

NDA 22-512

CMC Review No. 2

PRADAXA[®]
(Dabigatran etexilate) Capsules
75mg/110mg/150mg

Boehringer Ingelheim Pharmaceuticals, Inc.

Charles Jewell, Ph.D. (Review of Drug Substance)
Prafull Shiromani Ph.D. (Review of Drug Product)

Division of New Drug Quality Assessment I Branch 1
For Division of Cardiovascular and Renal Products

Review of Chemistry, Manufacturing, and Controls

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Chemistry Review Data Sheet

1. NDA 22-512
2. REVIEW #: 2
3. REVIEW DATE: 07-Sep-2010
4. REVIEWER: Prafull Shiromani Ph.D. and Charles Jewell Ph.D.

5. PREVIOUS DOCUMENTS:

| <u>Previous Documents</u> | <u>Document Date</u> |
|---------------------------|----------------------|
| NDA 22-512 | 15-Dec-2010 |

6. SUBMISSION(S) BEING REVIEWED:

| <u>Submission(s) Reviewed</u> | <u>Document Date</u> |
|--|----------------------|
| Drug Product (DP) Amendment 0054-Details on three stability batches of the new 110 mg capsule <div style="background-color: #cccccc; width: 300px; height: 15px; margin-left: 150px; margin-top: 5px;">(b) (4)</div> | 28-Apr-2010 |
| Drug Product Amendment 0112- Applicant's Responses to FDA IR Letter of 29-Jun-2010 (Drug Substance and Drug Product) and Post Approval Stability Protocol and Commitment | 15-Jul-2010 |
| Drug Product Amendment 0119- <div style="background-color: #cccccc; width: 100px; height: 15px; margin-left: 100px; margin-top: 5px;">(b) (4)</div> Conclusion included in P.3 | 21-Jul-2010 |
| Drug Product Amendment 0120-3 months stability data on the new 110 mg capsules | 22-Jul-2010 |
| Drug Product Amendment 0129-Revised DP Specification reflecting reducing the acceptance criterion of degradant <div style="background-color: #cccccc; width: 100px; height: 15px; margin-left: 100px; margin-top: 5px;">(b) (4)</div> from <div style="background-color: #cccccc; width: 40px; height: 15px; margin-left: 10px; margin-top: 5px;">(b) (4)</div> to <div style="background-color: #cccccc; width: 40px; height: 15px; margin-left: 10px; margin-top: 5px;">(b) (4)</div> | 29-Jul-2010 |

Chemistry Review Data Sheet

Drug Product Amendment –SDN 165 (eCTD
0164) Revised DP Specification due to FDA 03-Sep-2010
recommended dissolution specification

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.
Address: 900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877
Representative: Michelle Kliewer
Director, Regulatory Affairs
Telephone: (203) 791-6519

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: PRADAXA®
- b) Non-Proprietary Name (USAN): dabigatran etexilate mesylate
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Stroke Prevention in Atrial Fibrillation

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 75 mg, 110 mg & 150 mg

13. ROUTE OF ADMINISTRATION: Oral

Chemistry Review Data Sheet

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name (INN): Ethyl 3-[[[2-[[[4-

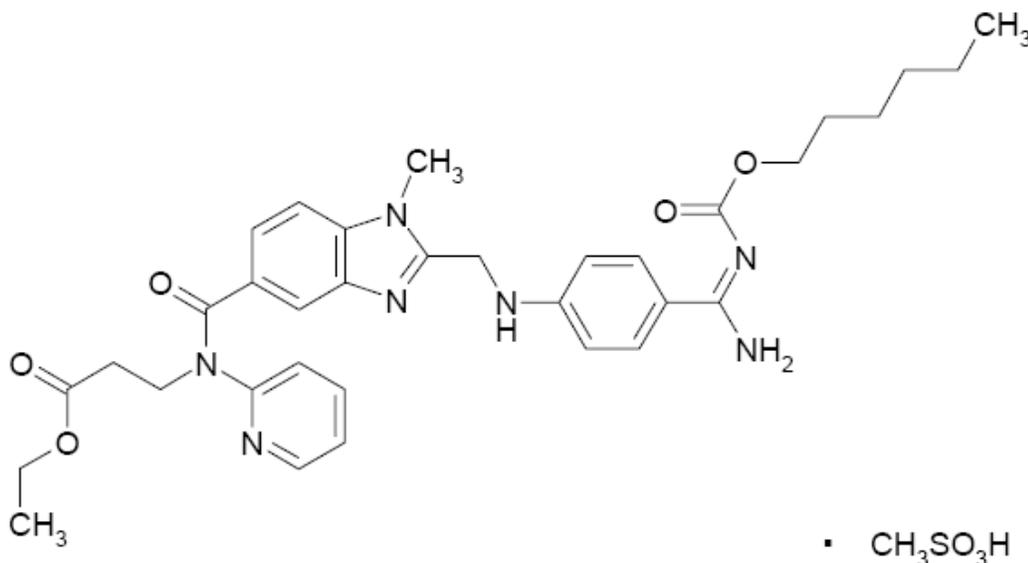
[[[(hexyloxy)carbonyl]amino]iminomethyl]phenyl]amino]methyl]-1-methyl-1*H*-benzimidazol-5-yl]carbonyl](pyridin-2-yl)amino]propanoate

Chemical Name (IUPAC): Ethyl *N*-{[2-({[4-((*E*)-amino {[(hexyloxy)carbonyl]imino} methyl)phenyl]amino} methyl)-1-methyl-1*H*-benzimidazol-5-yl]carbonyl}-*N*-pyridin-2-yl-β-alaninate methanesulfonate

Chemical Abstracts Name: beta-Alanine, *N*-[[2-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl]phenyl]amino] methyl]-1-methyl-1*H*-benzimidazol-5-yl]carbonyl]-*N*-2-pyridinyl-, ethyl ester, methanesulfonate

Chemical Name (JAN): Ethyl 3-({[2-({[4-(amino {[(hexyloxy)carbonyl]imino} methyl)phenyl]amino} methyl)-1-methyl-1*H*-benzimidazol-5-yl]carbonyl} (pyridin-2-yl)amino)propanoate monomethanesulfonate

Structural Formula:



Molecular Formula: C₃₄H₄₁N₇O₅ · CH₄O₃S

Molecular Weight (salt): 723.86 g/mol

Chemistry Review Data Sheet

Molecular Weight (free base): 627.75 g/mol

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|---|-------------------------------------|--------------------------------------|
| (b) (4) | III | (b) (4) | (b) (4) | 4 | N/A | | (b) (4) LOA Date: 10/30/08 |
| | III | | 4 | N/A | | (b) (4) LOA Date: 7/7/06 | |
| | III | | 4 | N/A | | (b) (4) LOA Date: 7/10 06 | |
| | IV | | 3 | Adequate | 20-Oct-2005; Dr. Y. Amin | LOA dated 03-Mar-2010 | |
| | IV | | 3 | Adequate | (b) (4) 12-Oct-2005; Dr Y. Amin. (b) (4) 11-Dec- 2009; Dr. Y. Sun. | LOA dated 15-Feb-2010 | |
| | IV | | 3 | Adequate | 11-Dec-2009: Dr. Y. Sun (refer to DMF (b) (4) above) | LOA dated 03-Sep-2009 | |
| | III | | 4 | N/A | | LOA dated 10-Feb-2009 | |
| | III | | 4 | N/A | | LOA dated 08-Sep-2008 | |

Chemistry Review Data Sheet

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|---------------------|-----------------------|-------------------------------------|
| (b) (4) | III | (b) (4) | (b) (4) | 4 | N/A | | (b) (4) LOA dated 17-Sep-2009 |
| | III | | | 4 | N/A | | LOA Dated 04-Aug-2009 |

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|-------------|
| | | |
| | | |
| | | |

18. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|----------------|-------------|----------|
| Biometrics | N/A | | |
| EES | Acceptable | 21-May-2010 | M. Stock |
| Pharm/Tox | | | |

Chemistry Review Data Sheet

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|---|---|--|
| Biopharm | The Biopharm reviewer recommends a Q = ^{(b) (4)} in 30 min as against Q = ^{(b) (4)} in 45 min | 18-Jun-2010 and FDA Letter of 01-Sep-2010 | T. Ghosh |
| LNC | | | |
| Methods Validation | Samples of the DS, DP and reference compounds are available. | | Validation is not required since the analytical methods are conventional |
| OPDRA | | | |
| EA | Acceptable-FONSI | 16-Jul-2010 | Raanan Bloom |
| Microbiology | N/A | | |

The Chemistry Review for NDA 22-512

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided adequate responses to the FDA IR letter sent on 29-Jun-2010. Additionally, the ONDQA Biopharm and Environmental Assessment reviews have been satisfactorily completed with no pending issues and are submitted into DARRTS. Accordingly, this NDA is recommended for approval from a CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Dabigatran etexilate mesylate [IUPAC Name: Ethyl *N*-{[2-({[4-((*E*)-amino{[(hexyloxy)carbonyl]imino}methyl)phenyl]amino}methyl)-1-methyl-1*H*-benzimidazol-5-yl]carbonyl}-*N*-pyridin-2-yl-β-alaninate methanesulfonate, or Company code name: BIBR 1048 MS] is an orally active pro-drug of BIBR 953 ZW, a novel, synthetic, specific, non-peptide thrombin inhibitor. After oral administration and absorption from the gastrointestinal tract, BIBR 1048 MS is converted by esterases into the active moiety BIBR 953 ZW. The esterases hydrolyze the hexyloxycarbonyl group to reveal the free amidine moiety and the ethyl ester is hydrolyzed to the free acid. Thus BIBR 953 is a "zwitter ion".

Dabigatran etexilate mesylate drug substance is a yellow-white or yellow crystalline powder. It is manufactured at 4 sites (2 of these sites are only involved with (b) (4) of the drug substance) by two manufacturing processes (referred to as (b) (4) and (b) (4)). Two (b) (4) anhydrous polymorphic forms and a (b) (4) form have been identified. Drug substance is composed of mostly the anhydrous form I, containing up to (b) (4) anhydrous form II and in the solid state they cannot be transformed into the (b) (4) form. The drug substance is described as BCS Class II, indicating poor aqueous solubility but good membrane permeability. Aqueous solubility is better at lower pH (pH less than 3) but the drug substance is virtually insoluble at neutral or basic pH. In both manufacturing processes the drug substance is (b) (4) to obtain (b) (4) particle size. This is required because (b) (4)

The polymorphic composition does not have any impact on the drug product manufacturing process, but it is controlled to (b) (4) form II because the bulk

Executive Summary Section

handling properties (b) (4) are significantly better for the polymorph form I especially on commercial scale.

Stability studies have established a retest date of (b) (4) for drug substance stored in appropriate containers to limit exposure to moisture. This is required to prevent (b) (4) degradation within the set limits.

Complete details of the drug substance are provided in CMC Review #1. This CMC review #2 pertains to the FDA CMC evaluation of the applicant's responses to the FDA IR Letter of 29-Jun-2010. With respect to the drug substance, there were two requests from the FDA. The applicant's responses were satisfactory. To summarize, the FDA requested the applicant to add testing to specifications for two reagents used in the manufacture of the drug substance. These added specifications would contribute to the control of potential genotoxic impurities which are possible from impurities introduced into the manufacturing stream due to these reagents. The two reagents are (b) (4) and (b) (4). These two reagents are used (b) (4).

The applicant adequately complied with the request by adding key limit tests to the overall the specifications of these reagents. The details of these minor changes are discussed in the body of the review.

Drug Product

Three strengths of the product, 75, 110 and 150 mg, have been developed as immediate release HPMC capsules for commercialization, with only the 110 mg and 150 mg potencies intended for the US market. The capsules differ in size for the 3 strengths (sizes 2, (b) (4), and 0 for the 75 mg, 110 mg and 150 mg strengths respectively). The strengths are also differentiated by the imprinting on the capsule body. The capsules are filled with yellowish pellets made from the drug substance and standard compendial excipients. The amount of pellets filled into hard shell capsules determines the dosage strength, with the potencies being weight multiples. Additional details on the drug product are provided in CMC Review # 1.

This CMC review # 2 pertains to FDA CMC evaluation of the applicant's responses to the FDA IR Letter of 29-Jun-2010. Their responses are satisfactory, a few of which are summarized below:

-They have provided a detailed response on the experimental design and statistical analysis employed to generate the (b) (4)

-They have provided details of their extensive FMEA (Failure Mode & Effect Analysis) risk assessment approach to assess potential risks in terms of RPN (Risk Priority Number) for each step of the manufacturing step – (b) (4)

Their manufacturing process has proven to be very robust yielding quality product.

-They have revised the FDA recommended acceptance criterion for the primary degradation product (b) (4) from NMT (b) (4) to NMT (b) (4) in their drug product specification for all strengths and packages and provided the revised drug product specification table.

(b) (4)

Executive Summary Section

(b) (4)

- The applicant has included the (b) (4) -presented in P.2.3 in the original NDA) information in section 3.2.P.3.3 - Amendment 0119, as requested by ONDQA (Science & Policy).

-In response to a comment in the FDA IR letter the applicant has reduced the acceptance criterion for the degradation product (b) (4) from (b) (4) to (b) (4) for both the bottle and the blister – Amendment # 0129, 29-Jul-2010

-Revised DP specification reflecting their acceptance of ONDQA Biopharm's dissolution specification of $Q = \frac{(b) (4)}{30}$ minutes; Amendment SDN 165 (eCTD: 0164), dated 03-Sep-2010 is included in this review.

B. Description of How the Drug Product is Intended to be Used

1. INDICATIONS AND USAGE

The product is intended for the prevention of stroke and systemic embolism and reduction of vascular mortality in patients with atrial fibrillation.

2. DOSAGE AND ADMINISTRATION

The recommended dosage of PRADAXA is 150 mg taken orally, twice daily. (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided adequate responses to the FDA IR letter, accordingly this NDA is recommended for approval from a CMC perspective.

III. Administrative

A. Reviewer's Signature

Executive Summary Section

B. Endorsement Block

Chemist Name/Date: Charles Jewell, Ph.D. and Prafull Shiromani, Ph.D.
September 7, 2010

ChemistryTeamLeaderName/Date: Rik Lostritto, Ph.D. September 7, 2010

ProjectManagerName/Date: Alison Blaus September 7,2010

C. CC Block

64 pp withheld in full immediately following 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/

CHARLES F JEWELL
09/07/2010

RICHARD T LOSTRITTO
09/15/2010

NDA 22-512

PRADAXA™ (dabigatran etexilate) Capsules

Boehringer Ingelheim Pharmaceuticals, Inc.

**Charles Jewell, Ph.D. (Review of Drug Substance)
Prafull Shiromani Ph.D. (Review of Drug Product)**

**Division of New Drug Quality Assessment I Branch 1
For Division of Cardiovascular and Renal Products**

Review of Chemistry, Manufacturing, and Controls

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Chemistry Review Data Sheet

1. NDA: 22-512
2. REVIEW#: 1
3. REVIEW DATE: June 29, 2010
4. REVIEWER: Charles Jewell, Ph.D., Prafull Shiromani, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

none

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Presubmission; eCTD # 0002 (Quality Section)
NDA 22-512
Drug Product Amendment 0054

Document Date

9/30/2009
15-Dec-2009
28-Apr-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.
Address: 900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877
Representative: Michelle Kliewer
Director, Regulatory Affairs
Telephone: (203) 791-6519

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: PRADAXA™
- b) Non-Proprietary Name (USAN): dabigatran etexilate mesylate

Chemistry Review Data Sheet

c) Code Name/# (ONDC only): N/A

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Stroke Prevention in Atrial Fibrillation

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 75 mg, 110 mg, 150 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name (INN): Ethyl 3-[[[2-[[[4-

[[[(hexyloxy)carbonyl]amino]iminomethyl]phenyl]amino]methyl]-1-methyl-1*H*-benzimidazol-5-yl]carbonyl](pyridin-2-yl)amino]propanoate

Chemical Name (IUPAC): Ethyl *N*-{2-({[4-((*E*)-

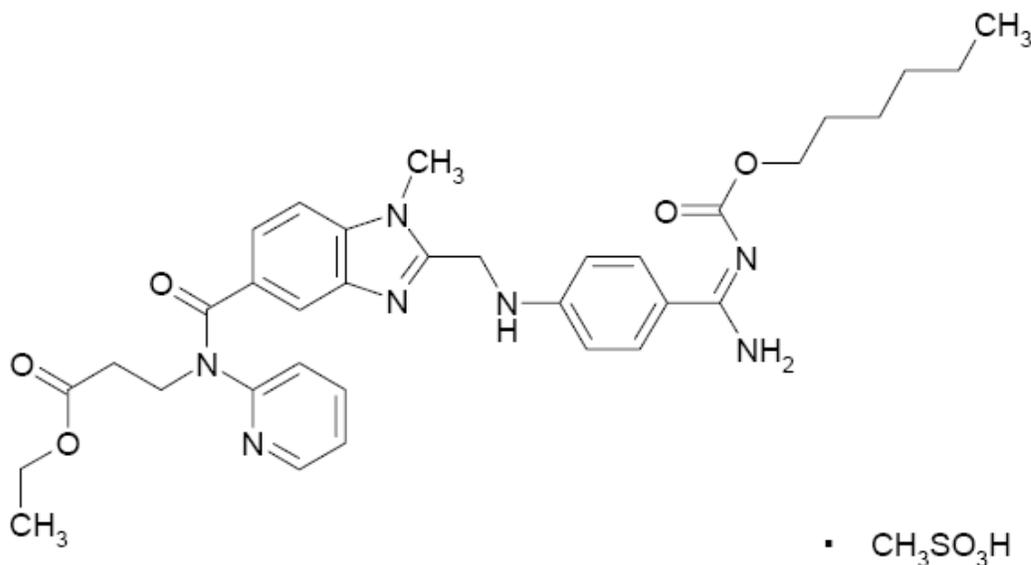
amino{[(hexyloxy)carbonyl]imino}methyl)phenyl]amino}methyl)-1-methyl-1*H*-benzimidazol-5-yl]carbonyl}-*N*-pyridin-2-yl-β-alaninate methanesulfonate

Chemical Abstracts Name: beta-Alanine, *N*-[[2-[[[4-

[[[(hexyloxy)carbonyl]amino]iminomethyl]phenyl]amino]methyl]-1-methyl-1*H*-benzimidazol-5-yl]carbonyl]-*N*-2-pyridinyl-, ethyl ester, methanesulfonate

Chemistry Review Data Sheet

Chemical Name (JAN): Ethyl 3-({[2-({[4-(amino{[(hexyloxy)carbonyl]imino}methyl)phenyl]amino}methyl)-1-methyl-1H-benzoimidazol-5-yl]carbonyl}(pyridin-2-yl)amino)propanoate monomethanesulfonate
 Structural Formula:



Molecular Formula: C₃₄H₄₁N₇O₅ · CH₄O₃S
 Molecular Weight (salt): 723.86 g/mol
 Molecular Weight (free base): 627.75 g/mol

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|------------|-----------------|-------------------|--|------------------------------|-------------------------------|
| (b) (4) | III | [REDACTED] | (b) (4) | 4 | N/A | | (b) (4) LOA Date: 10/30/08 |
| | III | | 4 | N/A | | (b) (4) LOA Date: 7/7/06 | |
| | III | | 4 | N/A | | (b) (4) LOA Date: 7/10 06 | |
| | IV | | 3 | Adequate | 20-Oct-2005; Dr. Y. Amin | LOA dated 03-Mar-2010 | |
| | IV | | 3 | Adequate | (b) (4) 12-Oct-2005; Dr Y. Amin. (b) (4) 11-Dec-2009; Dr. Y. Sun. | LOA dated 15-Feb-2010 | |
| | IV | | 3 | Adequate | 11-Dec-2009: Dr. Y. Sun (refer to DMF (b) (4) above) | LOA dated 03-Sep-2009 | |
| | III | | 4 | N/A | | LOA dated 10-Feb-2009 | |
| | III | | 4 | N/A | | LOA dated 08-Sep-2008 | |

Chemistry Review Data Sheet

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE ¹ | STATUS ² | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|--------|-----------------|-------------------|---------------------|-----------------------|-------------------------------------|
| (b) (4) | III | | (b) (4) | 4 | N/A | | (b) (4) LOA dated 17-Sep-2009 |
| | III | | | 4 | N/A | | LOA Dated 04-Aug-2009 |

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|-------------|
| | | |
| | | |
| | | |
| | | |

18. STATUS:

ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|-------------------------------|---|-------------|---|
| Biometrics | | | |
| EES | Overall Recommendation: Acceptable | 21-May-2010 | Summary report from EES pasted in review. |
| Pharm/Tox | Pending | | Pat Harlow |
| Biopharm | The Biopharm reviewer recommends a Q = (b) (4) in 30 min as against Q = (b) (4) in 45 min | 18-Jun-2010 | T. Ghosh |
| LNC | | | |

Chemistry Review Data Sheet

| | | | |
|--------------------|--|--|--|
| Methods Validation | Samples of the DS, DP and reference compounds are available. | | Validation is not required since the analytical methods are conventional |
| DMEPA | | | |
| EA | Pending | | |
| Microbiology | N/A | | |

The Chemistry Review for NDA 22-416

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA in its present form cannot be recommended for approval from a CMC perspective. The approval of this application, from a CMC perspective, depends on the applicant's response to the FDA CMC IR Letter.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Dabigatran etexilate mesylate [IUPAC Name: Ethyl *N*-{[2-({[4-((*E*)-amino {[(hexyloxy)carbonyl]imino}methyl)phenyl]amino}methyl)-1-methyl-1*H*-benzimidazol-5-yl]carbonyl}-*N*-pyridin-2-yl-β-alaninate methanesulfonate, or Company code name: BIBR 1048 MS] is an orally active pro-drug of BIBR 953 ZW, a novel, synthetic, specific, non-peptide thrombin inhibitor. After oral administration and absorption from the gastrointestinal tract, BIBR 1048 MS is converted by esterases into the active moiety BIBR 953 ZW. The esterases hydrolyze the hexyloxy carbonyl group to reveal the free amidine moiety and the ethyl ester is hydrolyzed to the free acid. Thus BIBR 953 is a "zwitter ion".

Dabigatran etexilate mesylate drug substance is a yellow-white or yellow crystalline powder. It is manufactured at 4 sites (2 of these sites are only involved with (b) (4) of the drug substance) by two manufacturing processes (referred to as (b) (4) and (b) (4)). Two (b) (4) anhydrous polymorphic forms and a (b) (4) form have been identified. Drug substance is composed of mostly the anhydrous form I, containing up to (b) (4) anhydrous form II and in the solid state they cannot be transformed into the (b) (4) form. The drug substance is described as BCS Class II, indicating poor aqueous solubility but good membrane permeability. Aqueous solubility is better at lower pH (pH less than 3) but the drug substance is virtually insoluble at neutral or basic pH. In both manufacturing processes the drug substance is (b) (4) to obtain (b) (4) particle size. This is required because the (b) (4)

The polymorphic composition does not have any impact on the drug product manufacturing process, but it is controlled to (b) (4) form II because the bulk handling properties (b) (4) are significantly better for the polymorph form I especially on commercial scale.

Executive Summary Section

(b) (4)

Standard test attributes for solid oral dosage forms have been proposed. Loss on drying is performed on both pellets and capsule shell. Uniformity of dosage units is tested by weight variation in accordance with USP <905> since the capsule contents are about (b) (4) by mass of the active ingredient. Dissolution testing is carried out in 0.01 M HCl using a basket apparatus at 100 rpm and sampling at 45 min. The Biopharm reviewer recommends a $Q = (b) (4)$ in 30 min as against $Q = (b) (4)$ in 45 min stated in the submission; furthermore, concludes that the sponsor's justification of the dissolution methodology including use of size-adjusted basket beyond 6 months for 150 mg tablet is acceptable.

Primary stability studies have been carried out on 3 batches of each strength. All nine primary batches were manufactured by the proposed (b) (4) commercial process at the proposed commercial site in Ingelheim. Dabigatran etexilate pellets used for the capsule batches were manufactured at pilot scale. Encapsulation of the pellets resulted in capsule batch sizes which are within the commercial batch size range. The batches were packaged in the proposed market packaging -6 count CR aluminum/aluminum blisters and polypropylene bottles with desiccant in the (b) (4) screw closure. 12

Executive Summary Section

months' long term and 6 months' accelerated data are available for all batches. Based on the data and statistical analysis, a 24 month expiration dating period for storage at 25°C is proposed for both bottles and blisters. Their shelf life proposal is acceptable based on ICH Q1E 2.4.1.1. In addition it is proposed that once the bottles are opened, the product should be used within 30 days.

(b) (4)

B. Description of How the Drug Product is Intended to be Used**1. INDICATIONS AND USAGE**

The product is intended for the prevention of stroke and systemic embolism and reduction of vascular mortality in patients with atrial fibrillation.

2. DOSAGE AND ADMINISTRATION

The recommended dosage of PRADAXA is 150 mg taken orally, twice daily.

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

Approvability will depend on the applicant's response to the following CMC comments on the Drug Substance and Drug Product:

Drug Substance Related:

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 an assay for (b) (4) and (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 an assay for (b) (4) and set appropriate limits in the specification for (b) (4)

Drug Product Related:*P.2.3: Manufacturing Process Development:*

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

Executive Summary Section

(b) (4)

P.8.2 Postapproval Stability Protocol and Stability Commitment:

16. 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:

17. 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:

18. 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".

Executive Summary Section

Dissolution

19. Your justification of the dissolution methodology including use of size-adjusted basket beyond 6 months 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) 1 (basket with adjusted (b) (4) 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.

- i. Provide dissolution data on stability at the 30 minute time point; if no such data is available then pull stability samples between 18 and 24 months and provide the 30 minute dissolution data.
- ii. Revise your stability protocol for your commitment/annual stability batches so as to conform to the above dissolution recommendation.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Charles Jewell, Ph.D. and Prafull Shiromani, Ph.D. June 28, 2010

ChemistryTeamLeaderName/Date: Rik Lostritto, Ph.D. June 28, 2010

ProjectManagerName/Date: Alison Blaus June 28,2010

C. CC Block

260 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) |

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

/s/

CHARLES F JEWELL
06/29/2010

PRAFULL K SHIROMANI
06/29/2010

RICHARD T LOSTRITTO
06/29/2010

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number: 22-512

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

Stamp Date: 19-April-2010

**Established/Proper Name: PRADAXA (dabigatran
etexilate mesylate)** **NDA Type: Commercial/Priority**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

| | Parameter | Yes | No | Comment |
|----|--|------------|-----------|---|
| 1 | On its face, is the section organized adequately? | X | | Rolling Review, Quality Sections in eCTD format, 3.2.S, 3.2.P, and 3.2.R with Lit. Ref. in 3.3. |
| 2 | Is the section indexed and paginated adequately? | X | | |
| 3 | On its face, is the section legible? | X | | |
| 4 | Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs? | X | | |
| 5 | Is a statement provided that all facilities are ready for GMP inspection? | X | | On 356h form with the 0002 submission |
| 6 | Has an environmental assessment report or categorical exclusion been provided? | X | | A 'consult' has been requested |
| 7 | Does the section contain controls for the drug substance? | X | | |
| 8 | Does the section contain controls for the drug product? | X | | |
| 9 | Has stability data and analysis been provided to support the requested expiration date? | X | | Drug Substance/Drug Product Stability and re-test date |
| 10 | Has all information requested during the IND phase, and at the pre-NDA meetings been included? | X | | For Drug Substance/Drug Product |
| 11 | Have draft container labels been provided? | X | | Electronic images included in application |
| 12 | Has the draft package insert been provided? | X | | Electronic images included |
| 13 | Has an investigational formulations section been provided? | X | | |
| 14 | Is there a Methods Validation | X | | |

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

| | | | | |
|----|---|--|---|--|
| | package? | | | |
| 15 | Is a separate microbiological section included? | | X | |

Have all DMF references been identified? Yes

| DMF # | TYPE | HOLDER | ITEM REFERENCED | LOA DATE | COMMENTS |
|---------|------|--------|-----------------|-------------|----------|
| (b) (4) | III | | (b) (4) | 30-Oct_2008 | (b) (4) |
| | III | | 07-Jul_2006 | (b) (4) | |
| | III | | 10-July-2006 | (b) (4) | |
| | IV | | 01-Sep-2009 | (b) (4) | |
| | IV | | 03-Sep-2009 | (b) (4) | |
| | | | 03-Sep-2009 | (b) (4) | |

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA is not fileable from the product quality perspective, state the reasons and provide comments to be sent to the Applicant. - Appears to be fileable from the CMC standpoint

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None for 74-day letter.

Charles F. Jewell/Prafull Shiromani

6/08/2010

Product Quality Reviewer

Date

Team Leader/Supervisor

Date

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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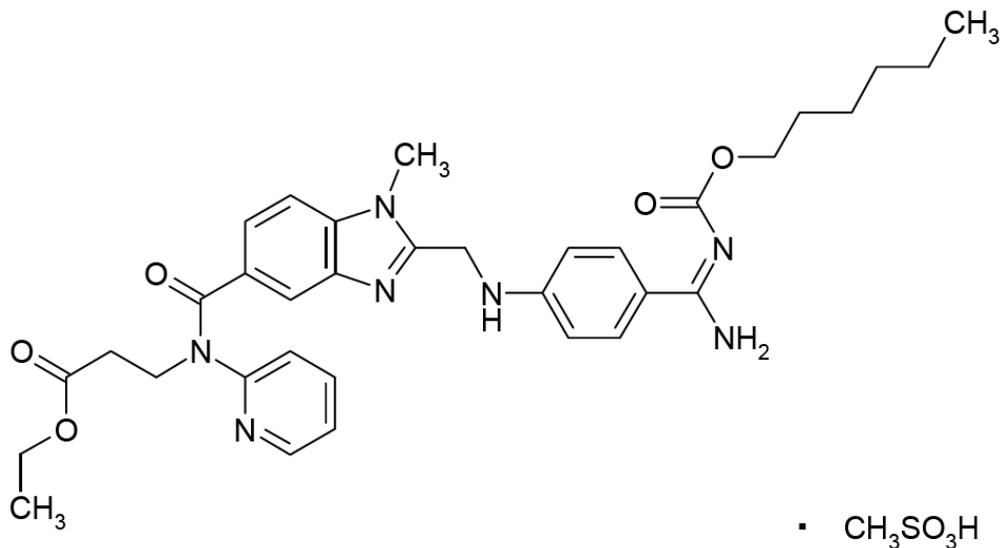
/s/

CHARLES F JEWELL
06/08/2010

RAMESH K SOOD
06/08/2010

Initial Quality Assessment Branch I

OND Division: Division of Cardiovascular and Renal Products
NDA: 22-512
Applicant: Boehringer Ingelheim
Letter Date: 15 Dec 2009
Stamp Date: 15 Dec 2009
PDUFA Date: 15 June 2010
Tradename: Pradaxa
Established Name: Dabigatran etexilate and dabigatran etexilate mesylate
Dosage Form: Capsules, 75mg, 110 mg and 150 mg
Route of Administration: Oral
Indication: Stroke prevention in atrial fibrillation
Assessed by: Kasturi Srinivasachar
ONDQA Fileability: Yes



Summary

This NDA is an eCTD submission for a new molecular entity, dabigatran etexilate mesylate, an oral direct thrombin inhibitor. Dabigatran etexilate mesylate is a pro-drug which is converted in vivo to the active moiety, dabigatran, by esterases. Clinical development was carried out under IND 65,813 and the efficacy and safety of Pradaxa is derived mainly from a large Phase 3 study comparing this drug with warfarin. This is a rolling submission and the complete CMC section (Mod. 3 and QOS) was submitted a few months prior to the official start date of Dec. 15, 2009. A number of meetings, CMC specific as well as interdisciplinary with CMC, were scheduled with the Sponsor but were cancelled based on the preliminary responses to their questions. These dealt with issues such as routine monitoring of (b) (4) impurities in drug substance and drug product batches, starting material designation and biowaiver requests for lower strengths of IVAX (UK approved) warfarin based on establishing bioequivalence of the 10 mg strength to the US approved product, Coumadin. A multi-disciplinary pre-NDA meeting was held with Boehringer on May 18, 2009 and a number of CMC issues were discussed. No response was given to the Applicant's proposal for a reduced stability design for the post-approval drug product commitment and annual batches since this was considered a review issue and would depend on adequate justification and supporting data in the NDA. Boehringer was also advised to continue testing for (b) (4) in production drug product stability batches and petition for discontinuing this test post-approval, if warranted. Finally, they were told to include blister packaging in their post-approval stability commitment if they intended to market the product in blisters.

Drug Substance

Dabigatran etexilate mesylate is a yellow-white or yellow crystalline powder with melting point $180 \pm 3^\circ\text{C}$. It is a synthetic compound with no chiral centers. It is practically insoluble in water but the solubility is strongly pH dependent with rather high solubility (b) (4) in 0.1 N HCl) and very poor solubility in neutral or basic media (b) (4) at pH 7.4). It is stated that this is a BCS class II compound. The drug substance can be manufactured by either of two synthetic routes—the (b) (4) synthesis or the (b) (4) synthesis. Two of the three starting materials proposed are the same for both routes and the third is similar in structure. Dabigatran etexilate mesylate exhibits polymorphism and two forms have been observed in both (b) (4) processes. Anhydrous form II is thermodynamically more stable than anhydrous form I, however, the latter was chosen for development because of its superior bulk processing properties in the synthesis. The (b) (4) step was optimized to routinely produce form I in both routes of synthesis but some form II could be formed under the processing conditions. It is stated that (b) (4) does not induce form II formation and that form conversion does not occur during drug substance storage. The drug product manufacturing process was optimized to limit the solid state conversion and it is claimed that there is no evidence of morphic form transformation during drug product storage. The Applicant states that bioequivalence has been established between drug product batches manufactured with form I drug substance and form II drug substance.

There is a comprehensive discussion of potential as well as actually observed impurities in the drug substance. The impurity profiles of drug substance from both synthetic routes are comparable except for one impurity, (b) (4), which is only observed in the (b) (4) process.

Multiple degradation sites have been identified in dabigatran etexilate which is mainly prone to hydrolytic cleavage. There is also a detailed assessment of potential genotoxic impurities belonging to different structural classes e.g. (b) (4)

The drug substance specification includes the standard test attributes as well as tests for particle size and polymorphism purity. Stability data are available for the drug substance manufactured by both synthetic routes – 3 primary full production scale batches of the (b) (4) synthesis manufactured at the proposed commercial site (Ingelheim, Germany) and 3 primary full production scale batches of the (b) (4) synthesis manufactured at the proposed commercial site ((b) (4) with (b) (4) at Ingelheim). 18 months of long term data and 6 months of accelerated data are provided for both (b) (4) batches. In addition, 6 months' data are available for 3 production scale batches of (b) (4) drug substance manufactured at the proposed alternate commercial site in Ingelheim. Since an alternate (b) (4) site in (b) (4) is proposed, 3 months' stability data have been generated on 3 production scale (b) (4) batches manufactured at (b) (4) and (b) (4) at (b) (4). A retest period of (b) (4) is proposed.

Drug Product

(b) (4)



Labeling

- Is the 75 mg strength proposed for marketing? The 356h form lists this strength and draft container labels are provided for it. This strength has also been included in the CMC section. However, the draft package insert lists only the 110 mg and 150 mg strengths.
- The statement on the container labels [REDACTED]^{(b) (4)} should be reversed to state “ Each capsule contains xx mg dabigatran etexilate mesylate equivalent to xx mg dabigatran etexilate”.

Comments and Recommendations

The application is fileable. Facilities have been entered into EES and the reviewers should verify the accuracy of the entries. This NDA contains fairly complex synthetic schemes for the drug substance and quality by design elements in the drug product section and it is recommended that reviewers with the appropriate background be assigned. A full environmental assessment report has been submitted and a consult request to OPS EA staff has been sent.

Kasturi Srinivasachar, Ph.D.
 Pharmaceutical Assessment Lead
Ramesh Sood, Ph.D.
 Branch Chief

Jan. 15, 2010
 Date
Jan. 15, 2010
 Date

| 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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