

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

22-512/S-011

Trade Name: PRADAXA

Generic Name: dabigatran etexilate mesylate

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date: 05/31/2012

Indications: PRADAXA is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

CENTER FOR DRUG EVALUATION AND RESEARCH

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-512/S-011

APPROVAL LETTER



NDA 22512/S-011

SUPPLEMENT APPROVAL

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

Dear Ms. Kliewer:

Please refer to your Supplemental New Drug Application (sNDA) dated January 24, 2012, received January 24, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Pradaxa (dabigatran etexilate mesylate) 75 and 150 mg Capsules.

We also acknowledge receipt of your amendment dated May 3, 2012.

This Prior Approval supplemental new drug application requested changes to the description of Pradaxa's efficacy findings relative to warfarin in RE-LY and labeling text on INR control in subject's randomized to warfarin in RE-LY.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text. The changes to Section 14, **CLINICAL STUDIES**, approved as part of this labeling supplement, are as follows:

1. The following sentence was edited:

“For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2 to 3) was 64%; the mean percentages of time INR measurements were greater than 4 or less than 1.5 were 2% and 5%, respectively.”

To appear as:

“For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2 to 3) was 64%.”

2. The following sentence was also edited:

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

To appear as:

“The treatment effect was primarily a reduction in stroke. PRADAXA 150 mg twice daily was superior in reducing ischemic and hemorrhagic strokes relative to warfarin.”

3. The following language and table were deleted from the **CLINICAL STUDIES** section:

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

Table 6 Center INR Control in the RE-LY Study

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

POSTMARKETING REQUIREMENTS UNDER 505(o)

We remind you of the following postmarketing requirement detailed in the PMR notification letter dated February 8, 2011:

- 1697-3 Relative bioavailability of a single dose of 150 mg dabigatran etexilate (capsule) when administered alone or in combination with a single dose of 400 mg dronedarone (tablet) or in combination with 400 mg bid dronedarone (tablet) at steady state in healthy male and female volunteers (an open label, randomized, four-sequence, two period cross-over, Phase I study)

The timetable you submitted on February 3, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2011
Trial Completion:	May 2011
Final Report Submission:	October 2011

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

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

If you have any questions, please contact Alison Blaus, Regulatory Project Manager, at (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

ENCLOSURE:
Content of Labeling

**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PRADAXA safely and effectively. See full prescribing information for PRADAXA.

PRADAXA® (dabigatran etexilate mesylate) capsules for oral use
Initial U.S. Approval: 2010

RECENT MAJOR CHANGES

Dosage and Administration (2.2, 2.4, 2.6) 1/2012
Warnings and Precautions (5.1, 5.2, 5.3) 1/2012

INDICATIONS AND USAGE

PRADAXA is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (1)

DOSAGE AND ADMINISTRATION

- For patients with CrCl >30 mL/min: 150 mg orally, twice daily (2.1)
- For patients with CrCl 15-30 mL/min: 75 mg orally, twice daily (2.1)
- Assess renal function during therapy as clinically indicated and adjust therapy accordingly (2.2)
- Instruct patients not to chew, break, or open capsules (2.3)
- Review recommendations for converting to or from other oral or parenteral anticoagulants (2.4, 2.5)
- Temporarily discontinue PRADAXA before invasive or surgical procedures when possible, then restart promptly (2.6)

DOSAGE FORMS AND STRENGTHS

Capsules: 75 mg and 150 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding (4)
- History of serious hypersensitivity reaction to PRADAXA (4)

WARNINGS AND PRECAUTIONS

- Risk of bleeding: PRADAXA can cause serious and, sometimes, fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.1)
- Temporary discontinuation: Avoid lapses in therapy to minimize risk of stroke (5.2)
- P-gp inducers and inhibitors: Effects on dabigatran exposure (5.3)

ADVERSE REACTIONS

Most common adverse reactions (>15%) are gastritis-like symptoms and bleeding (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- P-gp inducers rifampin: Avoid coadministration with PRADAXA (5.3)
- P-gp inhibitors dronedarone and systemic ketoconazole in patients with moderate renal impairment (CrCl 30-50 mL/min): Consider reducing PRADAXA dose to 75 mg twice daily (7)
- P-gp inhibitors in patients with severe renal impairment (CrCl <30 mL/min): PRADAXA use not recommended (7)

USE IN SPECIFIC POPULATIONS

Geriatric use: Risk of bleeding increases with age (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2012

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

For patients with creatinine clearance (CrCl) >30 mL/min, the recommended dose of PRADAXA is 150 mg taken orally, twice daily, with or without food. For patients with severe renal impairment (CrCl 15-30 mL/min), the recommended dose of PRADAXA is 75 mg twice daily [see *Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*]. Dosing recommendations for patients with a CrCl <15 mL/min or on dialysis cannot be provided.

2.2 Dosing Adjustments

Assess renal function prior to initiation of treatment with PRADAXA. Periodically assess renal function as clinically indicated (i.e., more frequently in clinical situations that may be associated with a decline in renal function) and adjust therapy accordingly. Discontinue PRADAXA in patients who develop acute renal failure while on PRADAXA and consider alternative anticoagulant therapy.

In patients with moderate renal impairment (CrCl 30-50 mL/min), concomitant use of the P-gp inhibitor dronedarone or systemic ketoconazole can be expected to produce dabigatran exposure similar to that observed in severe renal impairment. Consider reducing the dose of PRADAXA to 75 mg twice daily [see *Drug Interactions (7) and Clinical Pharmacology (12.3)*].

Generally, the extent of anticoagulation does not need to be assessed. When necessary, use aPTT or ECT, and not INR, to assess for anticoagulant activity in patients on PRADAXA [see *Warnings and Precautions (5.1) and Clinical Pharmacology (12.2)*].

2.3 Instructions to Patients

Instruct patients to swallow the capsules whole. Breaking, chewing, or emptying the contents of the capsule can result in increased exposure [see *Clinical Pharmacology (12.3)*].

If a dose of PRADAXA is not taken at the scheduled time, the dose should be taken as soon as possible on the same day; the missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose. The dose of PRADAXA should not be doubled to make up for a missed dose.

2.4 Converting from or to Warfarin

When converting patients from warfarin therapy to PRADAXA, discontinue warfarin and start PRADAXA when the INR is below 2.0.

When converting from PRADAXA to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:

- For CrCl ≥50 mL/min, start warfarin 3 days before discontinuing PRADAXA.
- For CrCl 30-50 mL/min, start warfarin 2 days before discontinuing PRADAXA.
- For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing PRADAXA.
- For CrCl <15 mL/min, no recommendations can be made.

Because PRADAXA can increase INR, the INR will better reflect warfarin's effect only after PRADAXA has been stopped for at least 2 days [see *Clinical Pharmacology (12.2)*].

2.5 Converting from or to Parenteral Anticoagulants

For patients currently receiving a parenteral anticoagulant, start PRADAXA 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).

For patients currently taking PRADAXA, wait 12 hours (CrCl ≥30 mL/min) or 24 hours (CrCl <30 mL/min) after the last dose of PRADAXA before initiating treatment with a parenteral anticoagulant [see *Clinical Pharmacology (12.3)*].

2.6 Surgery and Interventions

If possible, discontinue PRADAXA 1 to 2 days (CrCl ≥50 mL/min) or 3 to 5 days (CrCl <50 mL/min) before invasive or surgical procedures because of the increased risk of bleeding. Consider longer times for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required [see *Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

If surgery cannot be delayed, there is an increased risk of bleeding [see *Warnings and Precautions (5.1)*]. This risk of bleeding should be weighed against the urgency of intervention [see *Warnings and Precautions (5.2)*].

3 DOSAGE FORMS AND STRENGTHS

150 mg capsules with a light blue opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a cream-colored opaque body imprinted in black with "R150".

75 mg capsules with a cream-colored opaque cap imprinted in black with the Boehringer Ingelheim company symbol and a cream-colored opaque body imprinted in black with "R75".

4 CONTRAINDICATIONS

PRADAXA is contraindicated in patients with:

- Active pathological bleeding [see *Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].
- History of a serious hypersensitivity reaction to PRADAXA (e.g., anaphylactic reaction or anaphylactic shock) [see *Adverse Reactions (6.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Bleeding

PRADAXA increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension). Discontinue PRADAXA in patients with active pathological bleeding [see *Dosage and Administration (2.2)*].

Risk factors for bleeding include the use of other drugs that increase the risk of bleeding (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs). PRADAXA's anticoagulant activity and half-life are increased in patients with renal impairment [see *Clinical Pharmacology (12.2)*].

A specific reversal agent for dabigatran is not available. Dabigatran can be dialyzed (protein binding is low, with the removal of about 60% of drug over 2-3 hours); however the amount of data supporting this approach is limited. Activated prothrombin complex concentrates (aPCCs, e.g., FEIBA), or recombinant Factor VIIa, or concentrates of coagulation factors II, IX or X may be considered but their use has not been evaluated in clinical trials. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of dabigatran. Consider administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used.

5.2 Temporary Discontinuation of PRADAXA

Discontinuing anticoagulants, including PRADAXA, for active bleeding, elective surgery, or invasive procedures, places patients at an increased risk of stroke. Minimize lapses in therapy.

5.3 Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure

The concomitant use of PRADAXA with P-gp inducers (e.g. rifampin) reduces exposure to dabigatran and should generally be avoided [see *Clinical Pharmacology (12.3)*].

P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran [see *Clinical Pharmacology (12.3)*]. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.

Consider reducing the dose of PRADAXA to 75 mg twice daily when dronedarone or systemic ketoconazole is coadministered with PRADAXA in patients with moderate renal impairment (CrCl 30-50 mL/min). Avoid use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) [see *Drug Interactions (7) and Use in Specific Populations (8.6)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study provided safety information on the use of two doses of PRADAXA and warfarin [see *Clinical Studies (14)*]. The numbers of patients and their exposures are described in Table 1. Limited information is presented on the 110 mg dosing arm because this dose is not approved.

Table 1 Summary of Treatment Exposure in RE-LY

	PRADAXA 110 mg twice daily	PRADAXA 150 mg twice daily	Warfarin
Total number treated	5983	6059	5998
Exposure			
> 12 months	4936	4939	5193
> 24 months	2387	2405	2470
Mean exposure (months)	20.5	20.3	21.3
Total patient-years	10,242	10,261	10,659

Drug Discontinuation in RE-LY

The rates of adverse reactions leading to treatment discontinuation were 21% for PRADAXA 150 mg and 16% for warfarin. The most frequent adverse reactions leading to discontinuation of PRADAXA were bleeding and gastrointestinal events (i.e., dyspepsia, nausea, upper abdominal pain, gastrointestinal hemorrhage, and diarrhea).

Bleeding [see Warnings and Precautions (5.1)]

Table 2 shows the number of patients experiencing serious bleeding during the treatment period in the RE-LY study, with the bleeding rate per 100 patient-years (%). Major bleeds fulfilled one or more of the following criteria: bleeding associated with a reduction in hemoglobin of at least 2 grams per deciliter or leading to a transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ (intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding). A life-threatening bleed met one or more of the following criteria: fatal, symptomatic intracranial bleed, reduction in hemoglobin of at least 5 grams per deciliter, transfusion of at least 4 units of blood, associated with hypotension requiring the use of intravenous inotropic agents, or necessitating surgical intervention. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.

Table 2 Bleeding Events* (per 100 Patient-Years)

	PRADAXA 150 mg twice daily N (%)	Warfarin N (%)	Hazard Ratio (95% CI**)
Randomized patients	6076	6022	
Patient-years	12,033	11,794	
Intracranial hemorrhage	38 (0.3)	90 (0.8)	0.41 (0.28, 0.60)
Life-threatening bleed	179 (1.5)	218 (1.9)	0.80 (0.66, 0.98)
Major bleed	399 (3.3)	421 (3.6)	0.93 (0.81, 1.07)
Any bleed	1993 (16.6)	2166 (18.4)	0.91 (0.85, 0.96)

*Patients contributed multiple events and events were counted in multiple categories.

**Confidence interval

The risk of major bleeds was similar with PRADAXA 150 mg and warfarin across major subgroups defined by baseline characteristics, with the exception of age, where there was a trend towards a higher incidence of major bleeding on PRADAXA (hazard ratio 1.2, 95% CI: 1.0 to 1.4) for patients ≥ 75 years of age.

There was a higher rate of major gastrointestinal bleeds in patients receiving PRADAXA 150 mg than in patients receiving warfarin (1.6% vs. 1.1%, respectively, with a hazard ratio vs. warfarin of 1.5, 95% CI, 1.2 to 1.9), and a higher rate of any gastrointestinal bleeds (6.1% vs. 4.0%, respectively).

Gastrointestinal Adverse Reactions

Patients on PRADAXA 150 mg had an increased incidence of gastrointestinal adverse reactions (35% vs. 24% on warfarin). These were commonly dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) and gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, hemorrhagic erosive gastritis, and gastrointestinal ulcer).

Hypersensitivity Reactions

In the RE-LY study, drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock were reported in $< 0.1\%$ of patients receiving PRADAXA.

7 DRUG INTERACTIONS

The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided [see *Clinical Pharmacology* (12.3)].

P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran [see *Clinical Pharmacology* (12.3)]. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.

In patients with moderate renal impairment (CrCl 30-50 mL/min), consider reducing the dose of PRADAXA to 75 mg twice daily when administered concomitantly with the P-gp inhibitor dronedarone or systemic ketoconazole. The use of P-gp inhibitors (verapamil, amiodarone, quinidine, and clarithromycin) does not require a dose adjustment of PRADAXA. These results should not be extrapolated to other P-gp inhibitors [see *Warnings and Precautions* (5.3), *Use in Specific Populations* (8.6), and *Clinical Pharmacology* (12.3)].

The concomitant use of PRADAXA and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) should be avoided [see *Warnings and Precautions* (5.3), *Use in Specific Populations* (8.6), and *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women.

Dabigatran has been shown to decrease the number of implantations when male and female rats were treated at a dosage of 70 mg/kg (about 2.6 to 3.0 times the human exposure at maximum recommended human dose [MRHD] of 300 mg/day based on area under the curve [AUC] comparisons) prior to mating and up to implantation (gestation Day 6). Treatment of pregnant rats after implantation with dabigatran at the same dose increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition. Although dabigatran increased the incidence of delayed or irregular ossification of fetal skull bones and vertebrae in the rat, it did not induce major malformations in rats or rabbits.

8.2 Labor and Delivery

Safety and effectiveness of PRADAXA during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using PRADAXA in this setting [see *Warnings and Precautions* (5.1)].

Death of offspring and mother rats during labor in association with uterine bleeding occurred during treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with dabigatran at a dose of 70 mg/kg (about 2.6 times the human exposure at MRHD of 300 mg/day based on AUC comparisons).

8.3 Nursing Mothers

It is not known whether dabigatran is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRADAXA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of PRADAXA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in the RE-LY study, 82% were 65 and over, while 40% were 75 and over. The risk of stroke and bleeding increases with age, but the risk-benefit profile is favorable in all age groups [see *Warnings and Precautions* (5), *Adverse Reactions* (6.1), and *Clinical Studies* (14)].

8.6 Renal Impairment

No dose adjustment of PRADAXA is recommended in patients with mild or moderate renal impairment [see *Clinical Pharmacology* (12.3)]. Reduce the dose of PRADAXA in patients with severe renal impairment (CrCl 15-30 mL/min) [see *Dosage and Administration* (2.1, 2.2) and *Clinical Pharmacology* (12.3)]. Dosing recommendations for patients with CrCl < 15 mL/min or on dialysis cannot be provided.

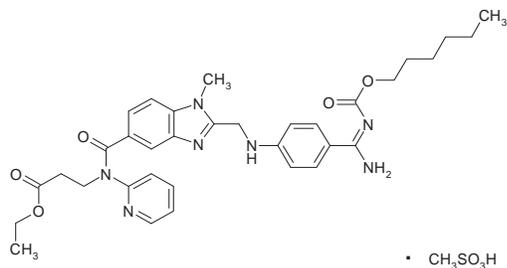
Adjust dose appropriately in patients with renal impairment receiving concomitant P-gp inhibitors [see *Warnings and Precautions* (5.3), *Drug Interactions* (7), and *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

Accidental overdose may lead to hemorrhagic complications. There is no reversal agent for dabigatran. In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment with PRADAXA, and investigate the source of bleeding. Dabigatran is primarily excreted in the urine and shows low plasma protein binding. Therefore, dabigatran can be dialyzed with the removal of about 60% of drug over 2 to 3 hours; however, data supporting this approach are limited. Measurement of aPTT or ECT may help guide therapy [see *Warnings and Precautions* (5.1) and *Clinical Pharmacology* (12.2)].

11 DESCRIPTION

The chemical name for dabigatran etexilate mesylate, a direct thrombin inhibitor, is β -Alanine, N-[[2-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl]phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methanesulfonate. The empirical formula is $C_{34}H_{41}N_7O_5 \cdot CH_3O_3S$ and the molecular weight is 723.86 (mesylate salt), 627.75 (free base). The structural formula is:



Dabigatran etexilate mesylate is a yellow-white to yellow powder. A saturated solution in pure water has a solubility of 1.8 mg/mL. It is freely soluble in methanol, slightly soluble in ethanol, and sparingly soluble in isopropanol.

The 150 mg capsule for oral administration contains 172.95 mg dabigatran etexilate mesylate, which is equivalent to 150 mg of dabigatran etexilate, and the following inactive ingredients: acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid. The capsule shell is composed of carrageenan, FD&C Blue No. 2 (150 mg only), FD&C Yellow No. 6, hypromellose, potassium chloride, titanium dioxide, and black edible ink. The 75 mg capsule contains 86.48 mg dabigatran etexilate mesylate, equivalent to 75 mg dabigatran etexilate, and is otherwise similar to the 150 mg capsule.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

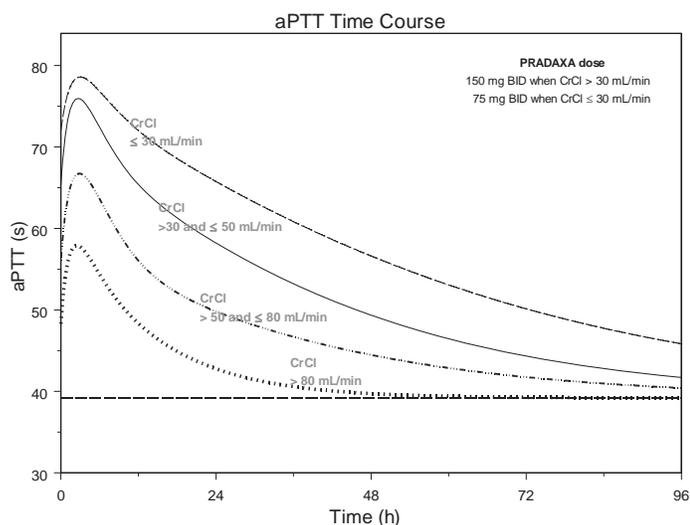
Dabigatran and its acyl glucuronides are competitive, direct thrombin inhibitors. Because thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited by the active moieties.

12.2 Pharmacodynamics

At recommended therapeutic doses, dabigatran etexilate prolongs the coagulation markers such as aPTT, ECT, and TT. INR is relatively insensitive to the exposure to dabigatran and cannot be interpreted the same way as used for warfarin monitoring.

The aPTT test provides an approximation of PRADAXA's anticoagulant effect. The average time course for effects on aPTT, following approved dosing regimens in patients with various degrees of renal impairment is shown in Figure 1. The curves represent mean levels without confidence intervals; variations should be expected when measuring aPTT. While advice cannot be provided on the level of recovery of aPTT needed in any particular clinical setting, the curves can be used to estimate the time to get to a particular level of recovery, even when the time since the last dose of PRADAXA is not precisely known. In the RE-LY trial, the median (10th to 90th percentile) trough aPTT in patients receiving the 150 mg dose was 52 (40 to 76) seconds.

Figure 1 Average Time Course for Effects of Dabigatran on aPTT, Following Approved PRADAXA Dosing Regimens in Patients with Various Degrees of Renal Impairment*



*Simulations based on PK data from a study in subjects with renal impairment and PK/aPTT relationships derived from the RE-LY study; aPTT prolongation in RE-LY was measured centrally in citrate plasma using PTT Reagent Roche Diagnostics GmbH, Mannheim, Germany. There may be quantitative differences between various established methods for aPTT assessment.

The degree of anticoagulant activity can also be assessed by the ecarin clotting time (ECT). This test is a more specific measure of the effect of dabigatran than activated partial thromboplastin time (aPTT). In the RE-LY trial, the median (10th to 90th percentile) trough ECT in patients receiving the 150 mg dose was 63 (44 to 103) seconds.

Cardiac Electrophysiology

No prolongation of the QTc interval was observed with dabigatran etexilate at doses up to 600 mg.

12.3 Pharmacokinetics

Dabigatran etexilate mesylate is absorbed as the dabigatran etexilate ester. The ester is then hydrolyzed, forming dabigatran, the active moiety. Dabigatran is metabolized to four different acyl glucuronides and both the glucuronides and dabigatran have similar pharmacological activity. Pharmacokinetics described here refer to the sum of dabigatran and its glucuronides. Dabigatran displays dose-proportional pharmacokinetics in healthy subjects and patients in the range of doses from 10 to 400 mg.

Absorption

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately 3 to 7%. Dabigatran etexilate is a substrate of the efflux transporter P-gp. After oral administration of dabigatran etexilate in healthy volunteers, C_{max} occurs at 1 hour post-administration in the fasted state. Coadministration of PRADAXA with a high-fat meal delays the time to C_{max} by approximately 2 hours but has no effect on the bioavailability of dabigatran; PRADAXA may be administered with or without food.

The oral bioavailability of dabigatran etexilate increases by 75% when the pellets are taken without the capsule shell compared to the intact capsule formulation. PRADAXA capsules should therefore not be broken, chewed, or opened before administration.

Distribution

Dabigatran is approximately 35% bound to human plasma proteins. The red blood cell to plasma partitioning of dabigatran measured as total radioactivity is less than 0.3. The volume of distribution of dabigatran is 50 to 70 L. Dabigatran pharmacokinetics are dose proportional after single doses of 10 to 400 mg. Given twice daily, dabigatran's accumulation factor is approximately two.

Elimination

Dabigatran is eliminated primarily in the urine. Renal clearance of dabigatran is 80% of total clearance after intravenous administration. After oral administration of radiolabeled dabigatran, 7% of radioactivity is recovered in urine and 86% in feces. The half-life of dabigatran in healthy subjects is 12 to 17 hours.

Metabolism

After oral administration, dabigatran etexilate is converted to dabigatran. The cleavage of the dabigatran etexilate by esterase-catalyzed hydrolysis to the active principal dabigatran is the predominant metabolic reaction. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Dabigatran is subject to conjugation forming pharmacologically active acyl glucuronides. Four positional isomers, 1-O, 2-O, 3-O, and 4-O-acylglucuronide exist, and each accounts for less than 10% of total dabigatran in plasma.

Renal Impairment

An open, parallel-group single-center study compared dabigatran pharmacokinetics in healthy subjects and patients with mild to moderate renal impairment receiving a single dose of PRADAXA 150 mg. Exposure to dabigatran increases with severity of renal function impairment (Table 3). Similar findings were observed in the RE-LY trial.

Table 3 Impact of Renal Impairment on Dabigatran Pharmacokinetics

Renal Function	CrCl (mL/min)	Increase in AUC	Increase in C_{max}	$t_{1/2}$ (h)
Normal	≥ 80	1x	1x	13
Mild	50-80	1.5x	1.1x	15
Moderate	30-50	3.2x	1.7x	18
Severe [†]	15-30	6.3x	2.1x	27

[†]Patients with severe renal impairment were not studied in RE-LY. Dosing recommendations in subjects with severe renal impairment are based on pharmacokinetic modeling [see *Dosage and Administration (2.1) and Use in Specific Populations (8.6)*].

Hepatic Impairment

Administration of PRADAXA in patients with moderate hepatic impairment (Child-Pugh B) showed a large inter-subject variability, but no evidence of a consistent change in exposure or pharmacodynamics.

Drug Interactions

Impact of Other Drugs on Dabigatran

P-gp Inducers

Rifampin Rifampin 600 mg once daily for 7 days followed by a single dose of dabigatran decreased its AUC and C_{max} by 66% and 67%, respectively. By Day 7 after cessation of rifampin treatment, dabigatran exposure was close to normal [see *Warnings and Precautions (5.3) and Drug Interactions (7)*].

P-gp Inhibitors

In studies with the P-gp inhibitors ketoconazole, amiodarone, verapamil, and quinidine, the time to peak, terminal half-life, and mean residence time of dabigatran were not affected. Any observed changes in C_{max} and AUC are described below.

Dronedarone Exposure to dabigatran is 73-99% higher when it is administered with dronedarone than when it is administered alone.

Ketoconazole: Systemic ketoconazole increased dabigatran AUC and C_{max} values by 138% and 135%, respectively, after a single dose of 400 mg, and 153%, and 149%, respectively, after multiple daily doses of 400 mg.

Verapamil: When dabigatran etexilate was coadministered with oral verapamil, the C_{max} and AUC of dabigatran were increased. The extent of increase depends on the formulation of verapamil and timing of administration. If verapamil is present in the gut when dabigatran is taken, it will increase exposure to dabigatran with the greatest increase observed when a single dose of immediate-release verapamil is given one hour prior to dabigatran (AUC increased by a factor of 2.4). If verapamil is given 2 hours after dabigatran, the increase in AUC is negligible. In the population pharmacokinetics study from RE-LY, no important changes in dabigatran trough levels were observed in patients who received verapamil.

Amiodarone: When dabigatran etexilate was coadministered with a single 600 mg oral dose of amiodarone, the dabigatran AUC and C_{max} increased by 58% and 50%, respectively. The increase in exposure was mitigated by a 65% increase in the renal clearance of dabigatran in the presence of amiodarone. The increase in renal clearance may persist after amiodarone is discontinued because of amiodarone's long half-life. In the population pharmacokinetics study from RE-LY, no important changes in dabigatran trough levels were observed in patients who received amiodarone.

Quinidine: Quinidine was given as 200 mg dose every 2 hours up to a total dose of 1000 mg. Dabigatran etexilate was given over 3 consecutive days, the last evening dose on Day 3 with or without quinidine pre-dosing. Concomitant quinidine administration increased dabigatran's AUC and C_{max} by 53% and 56%, respectively.

Clarithromycin Coadministered clarithromycin had no impact on the exposure to dabigatran.

Other Drugs

Clopidogrel: When dabigatran etexilate was given concomitantly with a loading dose of 300 mg or 600 mg clopidogrel, the dabigatran AUC and C_{max} increased by approximately 30% and 40%, respectively. The concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times compared to clopidogrel monotherapy. When comparing combined treatment and the respective mono-treatments, the coagulation measures for dabigatran's effect (aPTT, ECT, and TT) remained unchanged, and inhibition of platelet aggregation (IPA), a measurement of clopidogrel's effect, remained unchanged.

Enoxaparin Enoxaparin 40 mg given subcutaneously for 3 days with the last dose given 24 hours before a single dose of PRADAXA had no impact on the exposure to dabigatran or the coagulation measures aPTT, ECT, or TT.

Diclofenac, Ranitidine, and Digoxin None of these drugs alters exposure to dabigatran.

In RE-LY, dabigatran plasma samples were also collected. The concomitant use of proton pump inhibitors, H2 antagonists, and digoxin did not appreciably change the trough concentration of dabigatran.

Impact of Dabigatran on Other Drugs

In clinical studies exploring CYP3A4, CYP2C9, P-gp and other pathways, dabigatran did not meaningfully alter the pharmacokinetics of amiodarone, atorvastatin, clarithromycin, diclofenac, clopidogrel, digoxin, pantoprazole, or ranitidine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dabigatran was not carcinogenic when administered by oral gavage to mice and rats for up to 2 years. The highest doses tested (200 mg/kg/day) in mice and rats were approximately 3.6 and 6 times, respectively, the human exposure at MRHD of 300 mg/day based on AUC comparisons.

Dabigatran was not mutagenic in *in vitro* tests, including bacterial reversion tests, mouse lymphoma assay and chromosomal aberration assay in human lymphocytes, and the *in vivo* micronucleus assay in rats.

In the rat fertility study with oral gavage doses of 15, 70, and 200 mg/kg, males were treated for 29 days prior to mating, during mating up to scheduled termination, and females were treated 15 days prior to mating through gestation Day 6. No adverse effects on male or female fertility were observed at 200 mg/kg or 9 to 12 times the human exposure at MRHD of 300 mg/day based on AUC comparisons. However, the number of implantations decreased in females receiving 70 mg/kg, or 3 times the human exposure at MRHD based on AUC comparisons.

14 CLINICAL STUDIES

The clinical evidence for the efficacy of PRADAXA was derived from RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy), a multi-center, multi-national, randomized parallel group trial comparing two blinded doses of PRADAXA (110 mg twice daily and 150 mg twice daily) with open-label warfarin (dosed to target INR of 2 to 3) in patients with non-valvular, persistent, paroxysmal, or permanent atrial fibrillation and one or more of the following additional risk factors:

- Previous stroke, transient ischemic attack (TIA), or systemic embolism
- Left ventricular ejection fraction <40%
- Symptomatic heart failure, ≥ New York Heart Association Class 2
- Age ≥75 years
- Age ≥65 years and one of the following: diabetes mellitus, coronary artery disease (CAD), or hypertension

The primary objective of this study was to determine if PRADAXA was non-inferior to warfarin in reducing the occurrence of the composite endpoint, stroke (ischemic and hemorrhagic) and systemic embolism. The study was designed to ensure that PRADAXA preserved more than 50% of warfarin's effect as established by previous randomized, placebo-controlled trials of warfarin in atrial fibrillation. Statistical superiority was also analyzed.

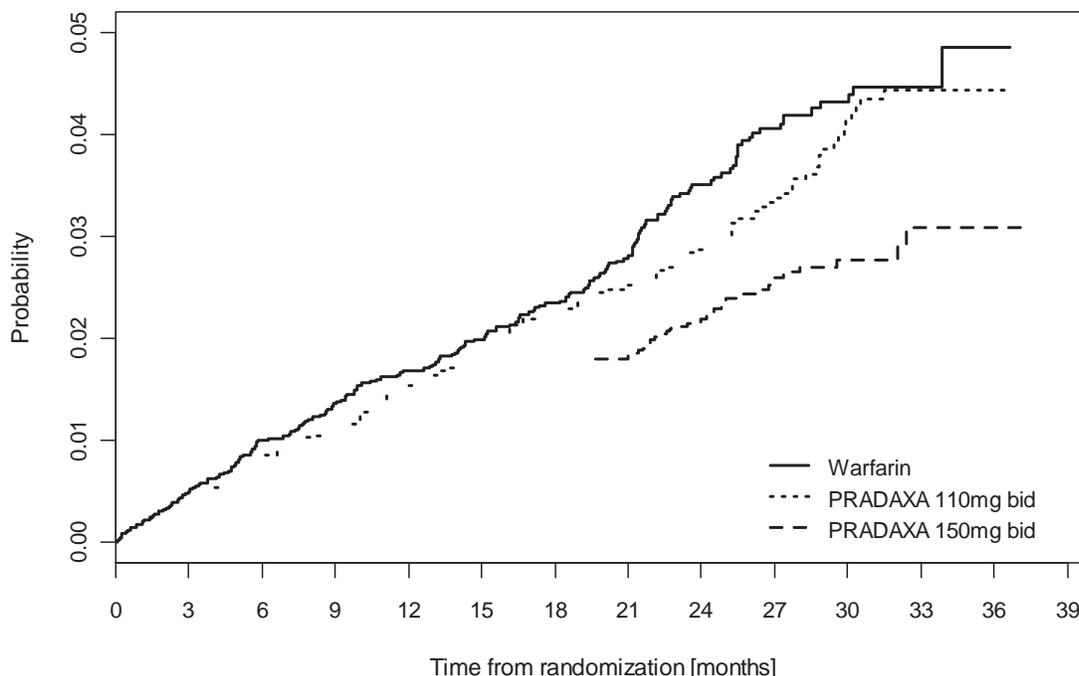
A total of 18,113 patients were randomized and followed for a median of 2 years. The patient's mean age was 71.5 years and the mean CHADS₂ score was 2.1. The patient population was 64% male, 70% Caucasian, 16% Asian, and 1% black. Twenty percent of patients had a history of a stroke or TIA and 50% were Vitamin K antagonist (VKA) naïve, defined as less than 2 months total lifetime exposure to a VKA. Thirty-two percent of the population had never been exposed to a VKA. Concomitant diseases of patients in this trial included hypertension 79%, diabetes 23%, and CAD 28%. At baseline, 40% of patients were on aspirin and 6% were on clopidogrel. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2 to 3) was 64%.

Relative to warfarin and to PRADAXA 110 mg twice daily, PRADAXA 150 mg twice daily significantly reduced the primary composite endpoint of stroke and systemic embolism (see Table 4 and Figure 2).

Table 4 First Occurrence of Stroke or Systemic Embolism in the RE-LY Study

	PRADAXA 150 mg twice daily	PRADAXA 110 mg twice daily	Warfarin
Patients randomized	6076	6015	6022
Patients (%) with events	134 (2.2%)	183 (3%)	202 (3.4%)
Hazard ratio vs. warfarin (95% CI)	0.65 (0.52, 0.81)	0.90 (0.74, 1.10)	
P-value for superiority	0.0001	0.3	
Hazard ratio vs. PRADAXA 110 mg (95% CI)	0.72 (0.58, 0.90)		
P-value for superiority	0.004		

Figure 2 Kaplan-Meier Curve Estimate of Time to First Stroke or Systemic Embolism



Patients at risk															
PRAD 110	6015	5927	5862	5797	5713	5481	4615	3778	3132	2383	1446	495	87		
PRAD 150	6076	6010	5940	5861	5782	5555	4700	3847	3238	2428	1481	494	90		
Warfarin	6022	5937	5862	5782	5719	5438	4615	3702	3092	2338	1364	383	76		

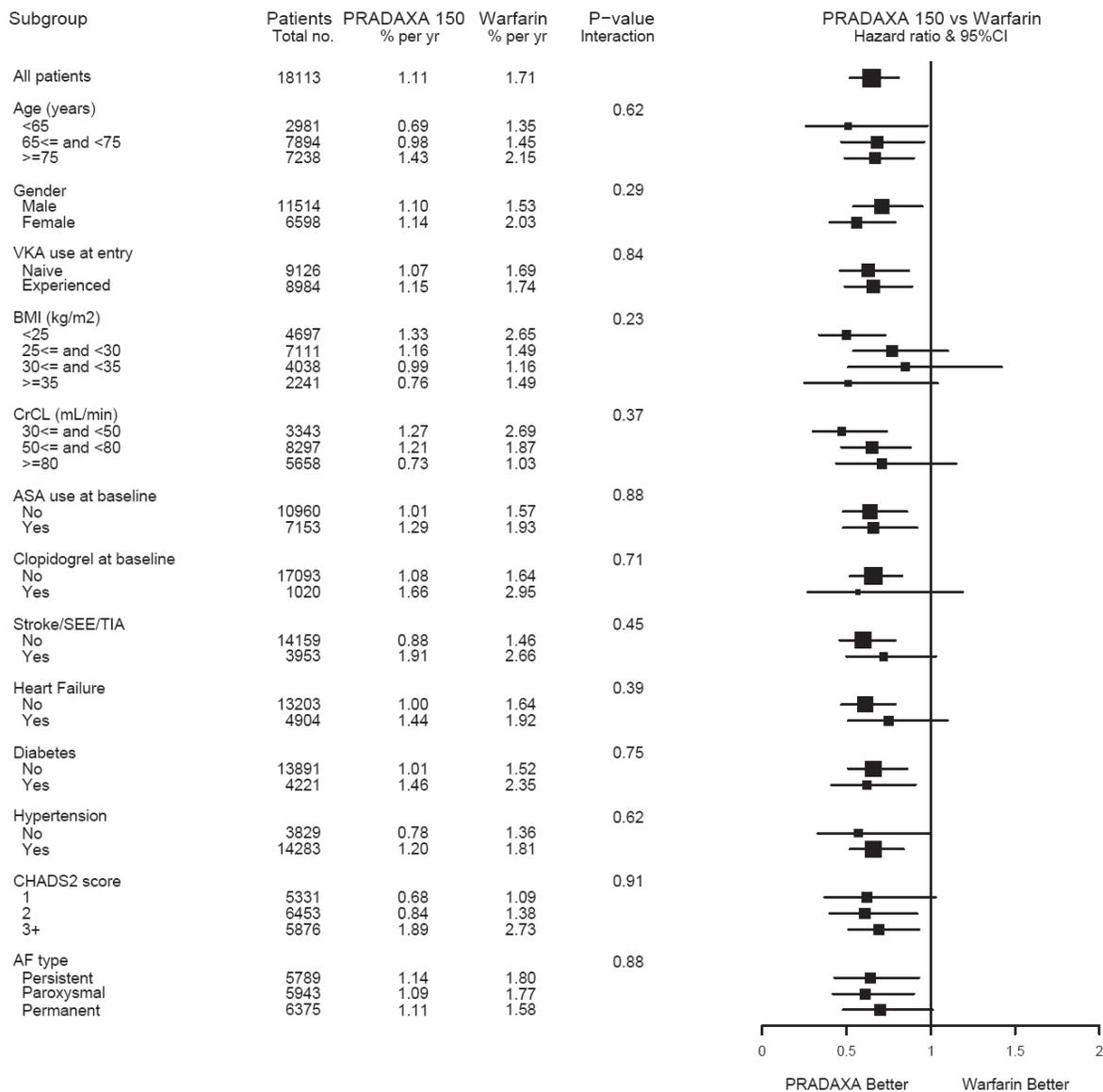
The contributions of the components of the composite endpoint, including stroke by subtype, are shown in Table 5. The treatment effect was primarily a reduction in stroke. PRADAXA 150 mg twice daily was superior in reducing ischemic and hemorrhagic strokes relative to warfarin.

Table 5 Strokes and Systemic Embolism in the RE-LY Study

	PRADAXA 150 mg twice daily	Warfarin	Hazard ratio vs. warfarin (95% CI)
Patients randomized	6076	6022	
Stroke	122	186	0.64 (0.51, 0.81)
Ischemic stroke	103	134	0.75 (0.58, 0.97)
Hemorrhagic stroke	12	45	0.26 (0.14, 0.49)
Systemic embolism	13	21	0.61 (0.30, 1.21)

The efficacy of PRADAXA 150 mg twice daily was generally consistent across major subgroups (see Figure 3).

Figure 3 Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics



In RE-LY, a higher rate of clinical myocardial infarction was reported in patients who received PRADAXA (0.7 per 100 patient-years for 150 mg dose) than in those who received warfarin (0.6).

16 HOW SUPPLIED/STORAGE AND HANDLING

PRADAXA 75 mg capsules have a cream-colored opaque cap imprinted with the Boehringer Ingelheim company symbol and a cream-colored opaque body imprinted with “R75”. The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0149-54 Unit of use bottle of 60 capsules
- NDC 0597-0149-60 Blister package containing 60 capsules (10 x 6 capsule blister cards)

PRADAXA 150 mg capsules have a light blue opaque cap imprinted with the Boehringer Ingelheim company symbol and a cream-colored opaque body imprinted with “R150”. The color of the imprinting is black. The capsules are supplied in the packages listed:

- NDC 0597-0135-54 Unit of use bottle of 60 capsules
- NDC 0597-0135-60 Blister package containing 60 capsules (10 x 6 capsule blister cards)

Bottles

Store at 25 C (77 F); excursions permitted to 15 -30 C (59 -86 F). Once opened, the product must be used within 4 months. Keep the bottle tightly closed. Store in the original package to protect from moisture.

Blisters

Store at 25 C (77 F); excursions permitted to 15 -30 C (59 -86 F). Store in the original package to protect from moisture.

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

17.1 Instructions for Patients

- Tell patients to take PRADAXA exactly as prescribed.
- Remind patients not to discontinue PRADAXA without talking to the health care provider who prescribed it.
- Keep PRADAXA in the original bottle to protect from moisture. Do not put PRADAXA in pill boxes or pill organizers.
- When more than one bottle is dispensed to the patient, instruct them to open only one bottle at a time.
- Instruct patient to remove only one capsule from the opened bottle at the time of use. The bottle should be immediately and tightly closed.
- Advise patients not to chew or break the capsules before swallowing them and not to open the capsules and take the pellets alone.

17.2 Bleeding

Inform patients that they may bleed more easily, may bleed longer, and should call their health care provider for any signs or symptoms of bleeding.

Instruct patients to seek emergency care right away if they have any of the following, which may be a sign or symptom of serious bleeding:

- Unusual bruising (bruises that appear without known cause or that get bigger)
- Pink or brown urine
- Red or black, tarry stools
- Coughing up blood
- Vomiting blood, or vomit that looks like coffee grounds

Instruct patients to call their health care provider or to get prompt medical attention if they experience any signs or symptoms of bleeding:

- Pain, swelling or discomfort in a joint
- Headaches, dizziness, or weakness
- Reoccurring nose bleeds
- Unusual bleeding from gums
- Bleeding from a cut that takes a long time to stop
- Menstrual bleeding or vaginal bleeding that is heavier than normal

17.3 Gastrointestinal Adverse Reactions

Instruct patients to call their health care provider if they experience any signs or symptoms of dyspepsia or gastritis:

- Dyspepsia (upset stomach), burning, or nausea
- Abdominal pain or discomfort
- Epigastric discomfort, GERD (gastric indigestion)

17.4 Invasive or Surgical Procedures

Instruct patients to inform their health care provider that they are taking PRADAXA before any invasive procedure (including dental procedures) is scheduled.

17.5 Concomitant Medications

Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take so their health care provider knows about other treatments that may affect bleeding risk (e.g., aspirin or NSAIDs) or dabigatran exposure (e.g., dronedarone or systemic ketoconazole).

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-512/S-011

MEDICAL REVIEW(S)



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: 25 May 2012
From: Aliza Thompson, M.D., Medical Officer
To: File
Subject: Dabigatran (NDA 22-512) and labeling pertaining to efficacy

Materials reviewed:

1. Boehringer Ingelheim submissions to NDA 22-512: prior approval labeling supplement (dated 24 January 2012) and general correspondence (dated 11 and 16 November 2011)

Dabigatran (Pradaxa), approved by FDA in October 2010, is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Pradaxa's efficacy and safety were demonstrated in a single, pivotal study (RE-LY) in which two doses of Pradaxa (110 and 150 mg) were compared with open label warfarin (targeted to an INR of 2 to 3). In RE-LY, the 150-mg dose of Pradaxa showed a statistically significant reduction in the risk of stroke and systemic embolism relative to warfarin and the 110 dose of Pradaxa. However, the current dabigatran label qualifies dabigatran's efficacy relative to warfarin by omitting direct reference to superiority in the Clinical Studies section of the label. The label also qualifies dabigatran's efficacy and safety findings via the inclusion of a post-hoc analysis of Center INR Control in the RE-LY study. The applicant believes that the RE-LY clinical trial data demonstrated that dabigatran 150 mg was superior in reducing strokes relative to warfarin and is seeking changes to the label in the context of the Agency's recent approval of rivaroxaban for the same indication. The current submissions include a prior approval labeling supplement and other correspondence providing the applicant's rationale for the proposed labeling changes.

Proposed changes to Section 14 Clinical Studies

1. Language related to the superiority of dabigatran over warfarin

Current text: PRADAXA 150 mg twice daily significantly reduced both ischemic and hemorrhagic strokes relative to warfarin.

Proposed text: PRADAXA 150 mg twice daily was superior in reducing (b) (4) ischemic and hemorrhagic strokes relative to warfarin.

2. Text/table on findings by center INR control

Proposed change: Deletion of Table 6 titled “Center INR Control in the RE-LY Study” and related text (shown below).

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

Table 6 Center INR Control in the RE-LY Study

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

3. Language on time in therapeutic range

Current text: For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2 to 3) was 64%; the mean percentages of time INR measurements were greater than 4 or less than 1.5 were 2% and 5%, respectively.

Proposed text: For patients randomized to warfarin, the (b) (4) percentage of time in therapeutic range (INR 2 to 3) was (b) (4).

Discussion of changes

Language related to the superiority of dabigatran over warfarin and text/table on findings by center INR control

The current dabigatran label qualifies dabigatran’s efficacy relative to warfarin by omitting direct reference to superiority in the Clinical Studies section of the label. Though several arguments were made against a superiority claim, the findings from post-hoc center-level TTR-based analyses factored heavily into the Agency’s decision to omit direct reference to superiority in dabigatran’s label. These analyses suggested a relationship between center-level INR control and the efficacy and safety of dabigatran relative to warfarin. The findings of these analyses were felt to be in keeping with analyses reported in the published literature that suggested that center-level TTR-based analysis might be useful for understanding whether the efficacy and safety findings in a trial of a new anticoagulant were being driven by less than ideal warfarin management. This trial level finding was also tied to a separate but related patient level issue—the concept that dabigatran might not provide greater efficacy in patients who were (or could be) well managed on warfarin.

Since dabigatran’s approval, the experience with other anticoagulants has raised questions about center-level TTR-based analyses and specifically whether they provide important insight into how the quality of warfarin management in a trial has impacted the trial’s efficacy findings.

Moreover, by currently available metrics (i.e., the mean time warfarin treated subjects were in therapeutic range), the level of INR control in warfarin treated subjects in RE-LY was reasonable. In RE-LY, the mean percentage of time in therapeutic range (INR 2 to 3) was 64%. When compared to warfarin as administered in RE-LY, dabigatran 150 mg twice daily caused a highly statistically significant reduction in strokes and systemic embolism (p-value for superiority of 0.0001). With regard to the components of the primary endpoint, dabigatran had a HR of 0.75 (0.58, 0.97) for ischemic stroke and a HR of 0.26 (0.14, 0.49) for hemorrhagic stroke when compared to warfarin. Hence, at this time, I think it is appropriate to revise labeling to indicate dabigatran's superiority to warfarin in RE-LY for the primary endpoint overall and the individual stroke components that were affected.

It is true that in any individual patient, dabigatran may not be superior to warfarin in reducing the risk of stroke or systemic embolism, particularly if that patient has or could achieve very good INR control on warfarin. However labeling describes the "on average" efficacy findings in a trial population; it is for practitioners to use the information contained in labeling to understand the likely benefits (and risks) of one therapy versus another in a given patient. A superiority claim does not guarantee superior efficacy (over another therapy) in all patients with a disease, just as an efficacy claim should not be taken as a guarantee of efficacy in all patients who receive a drug.

(b) (4)

(b) (4)

I think the applicant's request to delete the text on the mean percentages of time INR measurements were greater than 4 or less than 1.5 is reasonable. While the information may be accurate, I don't think it is particularly informative and certainly does not constitute essential scientific information needed for the safe and effective use of the drug (21CFR201.56). Of note, the rivaroxaban label does not contain this information.

Reviewer's Recommendations:

(b) (4)

The current text in Section 14 should be revised as follows "PRADAXA 150 mg twice daily ~~significantly reduced both~~ *was superior in reducing* ischemic and hemorrhagic strokes relative to warfarin." The other proposed changes should be adopted.

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/s/

ALIZA M THOMPSON
05/25/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-512/S-011

OTHER REVIEW(S)



DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

NDA: 22512

Supplement: 011

Drug: PRADAXA (dabigatran etexilate mesylate) Capsules

Class: direct thrombin inhibitor

Sponsor: Boehringer Ingelheim

Indication: No change in indication with this supplement

Date of submission: 24 January 2012

Goal date: 24 June 2012

❖ **REVIEW TEAM**

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

❖ **BACKGROUND**

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

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

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

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

❖ **REGULATORY TIMELINE**

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

❖ **LABELING NEGOTIATIONS**

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

1. The following sentence was edited:

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

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

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

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

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

Was edited to appear as the following:

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

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

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

Table 6 Center INR Control in the RE-LY Study

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

❖ **REVIEWS**

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

❖ **CONSULTS**

There were no consults associated with this supplement.

❖ **CONCLUSION**

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

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/s/

ALISON L BLAUS
05/29/2012

Prior Approval Supplement

APPEARS THIS WAY ON ORIGINAL

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/s/

SANDRA P MATTHEWS
01/31/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-512/S-011

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



NDA 22512/S-011

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ms. Michelle Kliewer
Director, Drug Regulatory Affairs
900 Ridgebury Rd.
Ridgefield, CT 06877

Dear Ms. Kliewer:

We have received your January 23, 2012, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA Number: 22512

Supplement Number: 011

Product Name: Pradaxa (dabigatran etexilate mesylate) Capsules, 75 mg and 150 mg

Date of Submission: January 23, 2012

Date of Receipt: January 24, 2012

This supplemental application proposed draft prescribing information for Pradaxa.

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 March 24, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly 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>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Please cite the application number listed above 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, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have 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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/s/

EDWARD J FROMM
01/31/2012