

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

22-512/S-004

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.

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APPLICATION NUMBER:

22-512/S-004

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APPLICATION NUMBER:

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APPROVAL LETTER



NDA 22512 / S-004

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 February 25, 2011, received February 25, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PRADAXA (dabigatran etexilate mesylate) 75 and 150 mg Capsules.

We also refer to our letter dated February 8, 2011, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for PRADAXA. This information pertains to the drug interaction between PRADAXA (dabigatran etexilate mesylate) and MULTAQ (dronedarone) that results in increased exposure to PRADAXA (dabigatran etexilate mesylate). Increased exposure to PRADAXA (dabigatran etexilate mesylate) may increase the risk of bleeding.

This supplemental new drug application provides for revisions to the labeling for PRADAXA, consistent with our February 8, 2011 letter. The addition to labeling, under Section 12.3/Drug Interactions/Impact of Other Drugs on Dabigatran/P-gp Inhibitors, is as follows:

“Dronedarone: Exposure to dabigatran is higher when it is administered with dronedarone than when it is administered alone (1.7- to 2-fold).”

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your February 25, 2011, submission includes final printed labeling (FPL) for your package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

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, 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(1)(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).

LETTERS TO HEALTH CARE PROFESSIONALS

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

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

REPORTING REQUIREMENTS

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

If you have any questions, please contact Alison Blaus, Regulatory Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

ALISON L BLAUS
03/04/2011

MARY R SOUTHWORTH
03/04/2011

**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

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)
• Instruct patients not to chew, break, or open capsules (2.1)
• Review recommendations for converting to or from other oral or parenteral anticoagulants (2.2, 2.3)
• Temporarily discontinue PRADAXA before invasive or surgical procedures when possible, then restart promptly (2.4)

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: Avoid coadministration of rifampin with PRADAXA because of 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.

USE IN SPECIFIC POPULATIONS
Geriatric use: Risk of bleeding increases with age (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: x/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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- 2 DOSAGE AND ADMINISTRATION**
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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 CrCl 15-30 mL/min, the recommended dose 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.

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.

2.2 Converting from or to Warfarin

When converting patients from warfarin therapy to PRADAXA, discontinue warfarin and start PRADAXA when the international normalized ratio (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 31-50 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 contribute to an elevated INR, the INR will better reflect warfarin's effect after PRADAXA has been stopped for at least 2 days.

2.3 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)*].

2.4 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)*]. Bleeding risk can be assessed by the ecarin clotting time (ECT). This test is a better marker of the anticoagulant activity of dabigatran than activated partial thromboplastin time (aPTT), prothrombin time (PT)/INR, or thrombin time (TT). If ECT is not available, the aPTT test provides an approximation of PRADAXA's anticoagulant activity [see *Clinical Pharmacology (12.2)*].

3 DOSAGE FORMS AND STRENGTHS

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" (150 mg) or "R75" (75 mg).

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. Risk factors for bleeding include the use of drugs that increase the risk of bleeding in general (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs) and labor and delivery. 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.

In the RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study, a life-threatening bleed (bleeding that met one or more of the following criteria: fatal, symptomatic intracranial, 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) occurred at an annualized rate of 1.5% and 1.8% for PRADAXA 150 mg and warfarin, respectively [see *Adverse Reactions (6.1)*].

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. Lapses in therapy should be avoided, and if anticoagulation with PRADAXA must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

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)*].

Reference ID: 2913530

P-gp inhibitors ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin do not require dose adjustments. These results should not be extrapolated to other P-gp inhibitors [see *Clinical Pharmacology (12.3)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The RE-LY 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

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

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 inhibitors ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin do not require dose adjustments. These results should not be extrapolated to other P-gp inhibitors [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

Reference ID: 2913530

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 has 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

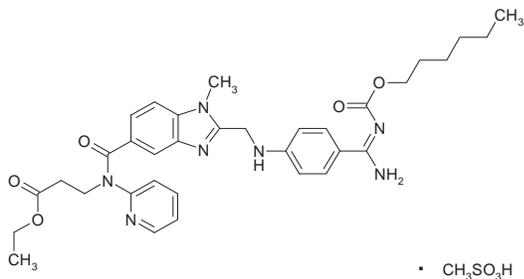
No dose adjustment of PRADAXA is recommended in patients with mild or moderate renal impairment. Reduce the dose of PRADAXA in patients with severe renal impairment (CrCl 15-30 mL/min) [see *Dosage and Administration (2.1)*]. Dosing recommendations for patients with CrCl <15 mL/min or on dialysis cannot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

10 OVERDOSAGE

Accidental overdose may lead to hemorrhagic complications. There is no antidote to dabigatran etexilate or 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; therefore, maintain adequate diuresis. Dabigatran can be dialyzed (protein binding is low), with the removal of about 60% of drug over 2 to 3 hours; however, data supporting this approach are limited. Consider surgical hemostasis or the transfusion of fresh frozen plasma or red blood cells. There is some experimental evidence to support the role of activated prothrombin complex concentrates (e.g., FEIBA), or recombinant Factor VIIa, or concentrates of coagulation factors II, IX or X; however, their usefulness in clinical settings has not been established. Consider administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used. Measurement of aPTT or ECT may help guide therapy [see *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 $C_{34}H_{41}N_7O_5 \cdot CH_4O_3S$ 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, 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

Reference ID: 2913530

At recommended therapeutic doses, dabigatran etexilate prolongs the aPTT, ECT, and TT. With an oral dose of 150 mg twice daily the median peak aPTT is approximately 2x control. Twelve hours after the last dose the median aPTT is 1.5x control, with less than 10% of patients exceeding 2x control. 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. The median (10th to 90th percentile) trough ECT in patients receiving the 150 mg dose was 63 (44 to 103) seconds. The INR test is relatively insensitive to the activity of dabigatran and may or may not be elevated in patients on PRADAXA. When converting a patient from PRADAXA to warfarin therapy, the INR is unlikely to be useful until at least 2 days after discontinuation of PRADAXA.

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. Co-administration 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. Based on pharmacokinetic modeling, estimated exposure to dabigatran increases with the severity of renal function impairment (Table 3). Similar findings were observed in the RE-LY trial.

Table 3 Estimated Pharmacokinetic Parameters of Dabigatran by Renal Function

Renal Function	CrCl (mL/min)	Increase in AUC	Increase in C _{max}	t _{1/2} (h)
Normal	80	1x	1x	13
Mild	50	1.5x	1.1x	15
Moderate	30	3.2x	1.7x	18

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 higher when it is administered with dronedarone than when it is administered alone (1.7- to 2-fold).

Ketoconazole: Ketoconazole increased dabigatran AUC_{0-∞} 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%; the mean percentages of time INR measurements were greater than 4 or less than 1.5 were 2% and 5%, respectively.

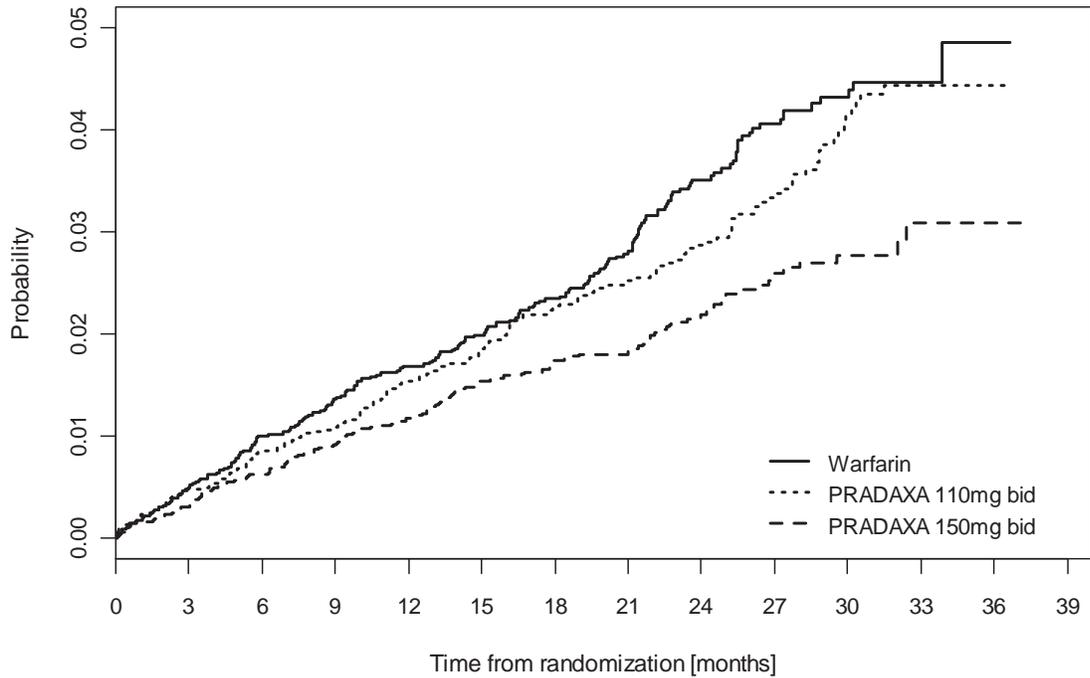
Relative to warfarin and to PRADAXA 110 mg twice daily, PRADAXA 150 mg twice daily significantly reduced the primary composite endpoint of stroke and systemic embolism (see Table 4 and Figure 1).

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		
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Figure 1 Kaplan-Meier Curve Estimate of Time to First Stroke or Systemic Embolism



Patients at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39
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	

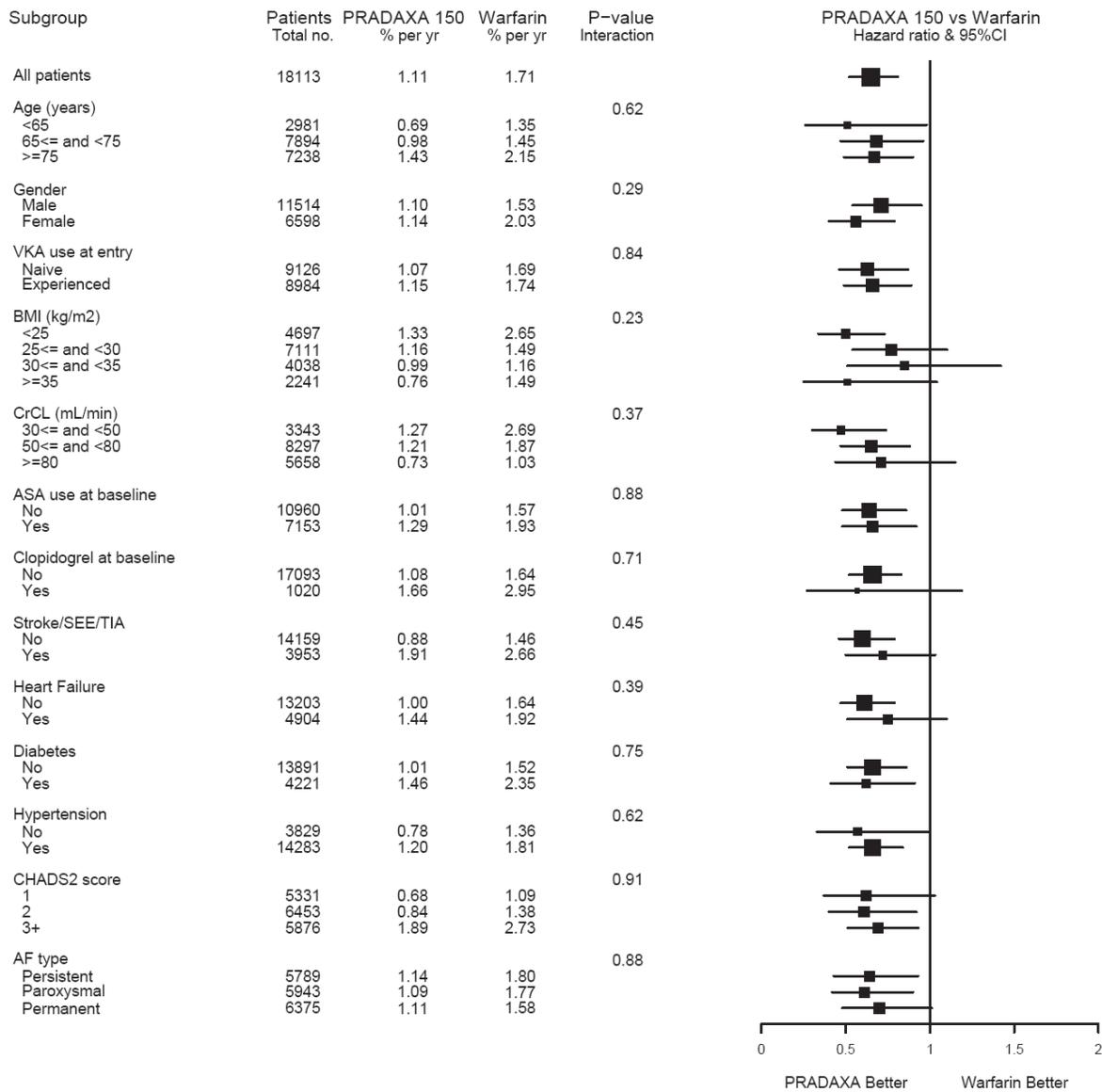
The contributions of the components of the composite endpoint, including stroke by subtype, are shown in Table 5. The treatment effect was primarily a reduction in stroke. PRADAXA 150 mg twice daily significantly reduced both ischemic and hemorrhagic strokes relative to warfarin.

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 2).

Figure 2 Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics



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)

The risk of myocardial infarction was numerically greater in patients who received PRADAXA (1.5% for 150 mg dose) than in those who received warfarin (1.1%).

16 HOW SUPPLIED/STORAGE AND HANDLING

PRADAXA 75 mg capsules have a light blue 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 0597-0107-54 Unit of use bottle of 60 capsules
- NDC 0597-0107-60 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)

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). 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 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 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.
- Advise patients not to chew or break the capsules before swallowing them and not to open the capsules and take the pellets alone (e.g., sprinkled over food or into beverages).

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.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-512/S-004

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: March 24, 2011

Application Type/Number: NDA 022512

To: Norman Stockbridge, MD, Director
Division of Cardiovascular and Renal Products

Through: Zachary Oleszczuk, Pharm.D., Team Leader
Kellie Taylor, Pharm.D., MPH, Associate Director
Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis

From: Manizheh Siahpoushan, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Pradaxa (Dabigatran Etexilate Mesylate) Capsules
75 mg and 150 mg

Applicant/sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2011-435, 2011-707

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1 INTRODUCTION

This review evaluates the container labels, carton and insert labeling for Pradaxa in response to a consult from the Division of Cardiovascular and Renal Products. In a recent article in ISMP's Medication Safety Alert on February 24, 2011, titled "*Pradaxa capsules have short expiration date after bottle opened*", ISMP noted that Pradaxa was only good for 30 days once opened and that capsules should remain in the original container. Additionally, during postmarketing surveillance, the Division of Pharmacovigilance (DPV1) discovered a case reported in AERS involving a patient who expressed concern over the lack of a tamper seal on the bottles containing Pradaxa and forwarded the case to DMEPA for evaluation.

1.1 REGULATORY HISTORY

Pradaxa was approved on October 19, 2010. There are special storage and product handling requirements associated with Pradaxa. Pradaxa capsules will hydrolyze over time when exposed to humidity, causing a breakdown of active ingredient and rendering the medication less effective. For this reason, Pradaxa was packaged in a 30-day supply bottle with a desiccant cap, and in unit-of-use blister packaging. However, since approval, there is new stability data available by the Applicant, that indicate there is no significant loss of potency up to 60 days after the bottle is opened, as long as Pradaxa is stored in the original bottle and the handling requirements are met.

2 METHODS

For this review, a search of the FDA Adverse Event Reporting System (AERS) database was conducted to evaluate errors involving Pradaxa labels and labeling since approval of Pradaxa on October 19, 2011.

Additionally, DMEPA evaluated the currently marketed container label, carton and package insert labeling, for Pradaxa using Failure Mode and Effects Analysis¹ (FMEA), principles of human factors, and lessons learned from the post marketing experience to identify areas that can contribute to medication errors.

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASSES

The DMEPA search of the FDA Adverse Event Reporting System (AERS) database on February 25, 2011 used the following search criteria: Active Ingredient "dabigatran extexilate mesylate, Trade Name "Pradaxa", verbatim terms "Prada%" and "dabig%", MedDRA reaction terms "Medication Errors" (HGLT), "Product Label Issues" (HLT), "Product Quality Issue" (PT), with no date limit.

Duplicate reports were combined into cases. Those cases, not pertaining to medication errors (e.g., adverse drug reactions, allergic reactions) or pertaining to medication errors due to concomitantly administered drugs were excluded from further analysis. All cases of medication error were evaluated and grouped by the type of error. Each case was evaluated for the root cause.

¹ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

2.2 LABELS AND LABELING RISK ASSESSMENT

Using Failure Mode and Effects Analysis² and the principals of Human Factors, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the currently marketed labels and labeling of the bottle labels to identify vulnerabilities that could lead to medication errors (see Appendix A). The blister labels and labeling was excluded since the possible hydrolysis that takes place, is not a problem with blister packs.

3 RESULTS AND DISCUSSIONS

The following sections describe the results of the DMEPA's medication error searches and labels and labeling evaluation.

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

The AERS search identified 24 reports. A list of ISR numbers is provided in Appendix B. After removing duplicate reports and cases not relevant to this review, as described in section 2.1, only one case remained which described a patient expressing concern over the fact that the bottle containing Pradaxa does not have a tamper seal and therefore can not determine if the bottle has been opened, and this raises concern over the 30 day expiration that exists for this product once opened.

In addition to our AERS search, the Institute of Safe Medication Practices (ISMP) contacted us regarding a case of name confusion between Pradaxa and Procardia. As reported in this case, Pradaxa 150 mg was listed on a patient's discharge drug list when they were sent to a nursing home. This order was confused with Procardia 150 mg in the skilled nursing facility. As a result of this error, the patient had to be readmitted to the hospital due to signs and symptoms of a stroke. This case provided no further details on the error. A search of the FDA's Adverse Event Reporting System (AERS) did not identify any similar cases of name confusion with Pradaxa. DMEPA notes the seriousness of this case and will continue to monitor for similar cases.

3.2 LABELS AND LABELING

Our evaluation of the container labels, carton and insert labeling identified areas of improvement that will help minimize the risk of medication errors associated with the current label and labeling for Pradaxa. We identified the following deficiencies:

- Lack of prominence of important storage requirements in the Medication Guide
- [REDACTED] (b) (4) on the Pradaxa bottle
- Absence of the important warning statement "Once opened, the product must be used within [REDACTED] (b) (4)." on the principal display panel
- Absence of the FD&C Yellow No. 6 warning on the carton and container labels

4 RECOMMENDATIONS

Our evaluation of the container labels, carton and insert labeling identified areas of needed improvement in order to increase awareness of the short expiry as well as the special storage requirements associated with Pradaxa. We provide recommendations for the insert labeling and container closure in Section 4.1 for discussion with the review team. We request the

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

recommendations for the container labels and carton labeling in Section 4.2 be communicated to the Applicant.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Nina Ton at 301-796-1648.

4.1 COMMENTS TO THE DIVISION

A. Insert Labeling

Under *Warnings and Precautions* sections in Highlights and Full Prescribing Information as well as *Instructions for Patients* under *Patient Counseling Information*, we recommend adding the statement “Once the bottle is opened, the product must be used within (b) (4).” Including the statement will make the warning more noticeable to both health care professionals and patients.

B. Medication Guide

Revise the section “How should I store Pradaxa?” to (b) (4) of “use Pradaxa within 30 days” by (b) (4) the statement, and add the statement “Store Pradaxa in the original package”. Additionally, the statement should be revised to reflect the new expiry period of (b) (4).

C. Container Closure

1. We recommend the applicant develop a (b) (4).
2. Consider (b) (4).

4.2 COMMENTS TO THE APPLICANT

A. Carton Labels (75 mg and 150 mg)

1. Relocate the statement “Usual Dosage: See package insert for dosage information.” to the side panel to create space for the important warning statement “Once opened, the product must be used within (b) (4).”
2. Relocate and bold the statement “Once opened, the product must be used within (b) (4).” to appear in conjunction with “Swallow capsule whole” on the principal display panel.
3. Relocate the net quantity statement “60 capsules” further down on the display panel to create more space for the warning statements “Swallow capsule whole”, “Once opened, the product must be used within (b) (4).”
4. Include the statement “Contains FD&C Yellow No. 6 as a color additive” on the side panel. The presence of such statement should be declared on the carton and container labels to comply with CFR 201.20 (c) as FD&C No. 6 is listed as one of the inactive ingredients in the Medication Guide.

B. Container Labels (75 mg and 150 mg)

1. Relocate and bold the statement “Once opened, the product must be used within (b) (4).” to appear in conjunction with “Swallow capsule whole” on the principal display panel.

2. Move “Rx only” to side panel to create white space on the principal display panel so warning statements can be more prominent.
3. Move Boehringer Ingelheim Logo to side panel or delete, and repeat statement “Store in original package” on the principal display panel.
4. Refer to comment 4.2- A4 above.

APPENDICES

APPENDIX A: Carton and Container Labels

Carton Labeling 75 mg Capsules



Carton Labeling 150 mg Capsules



Container Label 75 mg Capsules

NDC 0597-0107-54 60 capsules

DISPENSE IN THIS UNIT OF USE CONTAINER WITH ENCLOSED MEDICATION GUIDE

Pradaxa[®]
(dabigatran etexilate)
Capsules

75 mg*

Swallow capsule whole.
Rx only

 **Boehringer Ingelheim**

*Each capsule contains 86.48 mg dabigatran etexilate mesylate equivalent to 75 mg dabigatran etexilate.

Usual Dosage: See package insert for dosage information.

Store at 25°C (77°F) (see insert). Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

Once opened, the product must be used within 30 days.

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L5081A 76155-02 Lot Exp.

 0597-0107-54 5



Container Label 150 mg Capsules

NDC 0597-0135-54 60 capsules

DISPENSE IN THIS UNIT OF USE CONTAINER WITH ENCLOSED MEDICATION GUIDE

Pradaxa[®]
(dabigatran etexilate)
Capsules

150 mg*

Swallow capsule whole.
Rx only

 **Boehringer Ingelheim**

*Each capsule contains 172.95 mg dabigatran etexilate mesylate equivalent to 150 mg dabigatran etexilate.

Usual Dosage: See package insert for dosage information.

Store at 25°C (77°F) (see insert). Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

Once opened, the product must be used within 30 days.

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L5084A 76157-02 Lot Exp.

 0597-0135-54 8



APPENDIX B: ISR'S Listings from AERS Database

7216273	7211220
7272368	7234374
7127983	7234379
7146126	7236168
7148646	7273056
7148647	7273466
7148648	7273803
7148652	7286146
7231065	7307524
7285969	7287722
7209287	7312437
7210821	7271575*

*Signal case

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