

Graphic Packaging Intended to Deter Smoking

BY MICHELE G. SULLIVAN

The Food and Drug Administration has unveiled the final nine warning images that will appear on cigarette packages by 2012 – graphic photos and drawings intended to educate and even deter consumers from buying cigarettes.

The images are required by the 2009 Tobacco Control Act, according to FDA

spokesman Jeffrey Ventura, who added that these are the first changes to cigarette pack warnings in 25 years. By Oct. 22, 2012, cigarette manufacturers will no longer be able to distribute cigarettes for sale in the United States unless they display these warnings.

The law required the warnings to cover the top half of the front and back of cigarette packs and 20% of cigarette advertisements, and they must contain col-

or graphics depicting the negative health consequences of smoking.

“This is something Congress wanted to happen and mandated that the FDA carry out,” Mr. Ventura said in an interview. Based on a study of 18,000 smokers conducted for the FDA by RTI International, federal officials said they firmly believe that visually communicating smoking’s harm will deter cigarette consumption over the long run.

The images include tobacco-diseased lungs beside healthy lungs, a corpse in casket, a man exhaling smoke through a tracheostomy, and lip cancer. There are also several cartoons and photos of mothers blowing smoke into infants’ faces. One positive image shows a burly man exposing a T-shirt saying, “I Quit.” Blunt statements accompany each image, intended to drive home the messages that cigarette smoke not only directly harms the smoker, but the smokers’ children and people in close proximity.

“The introduction of these warnings is expected to have a significant public health impact by decreasing the number of smokers, resulting in lives saved, increased life expectancy, and improved health status,” FDA officials said in a statement.

“Eliciting strong emotional and cognitive reactions to the graphic cigarette warning label enhances recall and processing of the health warning, which helps ensure that the



Any one of nine images must appear on cigarette packs by Oct. 22, 2012.

warning is better processed, understood, and remembered,” the study said. “As attitudes and beliefs change, they eventually lead to changes in intentions to quit or start smoking and then later to lower smoking initiation and successful cessation. The time scale on which this behavior change process occurs is largely unknown in the context of the impact of exposure to graphic warning labels on smoking behaviors, but the effects on behavior change are unlikely to be immediate or short-term.”

Nevertheless, groups promoting anti-tobacco messages – including the American Heart Association – strongly believe that the warnings will enhance consumer education and change behavior.

“Undoubtedly, the new graphic health warnings will heighten awareness about the dangers of smoking and, more importantly, encourage smokers to quit and discourage smoking initiation,” an AHA press statement read. “We’re confident that the new labels will move us closer to our goal of making the nation 100% smoke free.”

PRADAXA® (dabigatran etexilate mesylate) capsules for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Rx only

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

PRADAXA is contraindicated in patients with:

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

WARNINGS AND PRECAUTIONS

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]. **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. **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. 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.

ADVERSE REACTIONS

Clinical Trials Experience: The RE-LY study provided safety information on the use of two doses of PRADAXA and warfarin. 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]:** 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)

(Table 2, Cont'd.)	PRADAXA 150 mg twice daily N (%)	Warfarin N (%)	Hazard Ratio (95% CI)**
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. 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%).

DRUG INTERACTIONS

The concomitant use of PRADAXA with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided. 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.

USE IN SPECIFIC POPULATIONS

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. **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]. 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). **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. **Pediatric Use:** Safety and effectiveness of PRADAXA in pediatric patients has not been established. **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 and Adverse Reactions]. **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). Dosing recommendations for patients with CrCl <15 mL/min or on dialysis cannot be provided.

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.

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