First oral thrombin inhibitor enters market

Drug does not require clinicians to monitor INR

FDA on October 19 approved the marketing of dabigatran etexilate, or Pradaxa, as a preventive to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Boehringer Ingelheim Pharmaceuticals Inc. said the new drug, when taken at a dosage of 150 mg twice daily in a large study, outdid standard-of-care warfarin in preventing stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Patients receiving dabigatran etexilate, FDA said, do not need to undergo the periodic blood monitoring that warfarin users do.

But like warfarin, dabigatran etexilate puts patients at risk of serious bleeding, the agency warned.

That risk is explained to patients in the FDA-approved medication guide and to health care professionals in the product’s labeling.

“I think this is an enormous advance in terms of offering an alternative to warfarin,” Ann K. Wittkowsky, director of anticoagulation services at 450-bed University of Washington Medical Center in Seattle, said of the new drug.

At 621-bed Beth Israel Deaconess Medical Center in Boston, Snehal B. Bhatt said the new drug seems an “attractive” alternative for warfarin users whose International Normalized Ratio (INR) tends not to stay within the target range.

Not an alternative for everyone. Bhatt, who participates in the cardiology service’s rounds and serves on the medical center’s anticoagulation subcommittee, said he would probably rule out from dabigatran etexilate therapy any patient with a creatinine clearance (\( \text{CL}_{\text{cr}} \)) of \( \leq 30 \) mL/min.

Both he and Wittkowsky expressed concern about the FDA-approved dosage recommendation of 75 mg twice daily for patients whose \( \text{CL}_{\text{cr}} \) is 15–30 mL/min.

That dosage, the two clinicians said, was not studied in any of the clinical trials.

And that type of patient, according to information available October 28 at ClinicalTrials.gov, was excluded from all Phase III studies of the drug.

The product labeling for dabigatran states that the drug is primarily eliminated in the urine.

No recommendations are given in the labeling for dosing dabigatran etexilate in patients with a \( \text{CL}_{\text{cr}} \) of <15 mL/min or who are undergoing dialysis.

Bhatt said he would probably not recommend dabigatran etexilate therapy for patients with a history of peptic ulcer disease or gastroesophageal reflux disease.

“Dyspepsia was 12% in the atrial fibrillation study,” he said, “and that is only going to be higher in the real world.”

The study to which Bhatt referred is known as Randomized Evaluation of Long-Term Anticoagulation Therapy With Dabigatran Eteixlate, or RE-LY.

Results of the company-funded study, involving 18,113 patients with nonvalvular atrial fibrillation and a risk of stroke, were reported in the September 17, 2009, issue of the New England Journal of Medicine.

Dyspepsia occurred in 11.5% of the patients who received 150 or 110 mg twice daily of dabigatran etexilate and 5.8% of the patients who received adjusted dosages of warfarin. The target INR range for the warfarin treatment group was 2.0–3.0.

At the start of the study, nearly 14% of the patients in each treatment group were taking a proton-pump inhibitor and roughly 4% were taking a histamine H2-receptor antagonist.

Patients who had had gastrointestinal bleeding during the previous year or gastroduodenal ulcer disease in the previous 30 days were excluded from the study.

The researchers also reported that about 20% of the people in the dabigatran groups had stopped receiving the drug by the year-2 follow-up visit.

“That’s one in five,” Bhatt said. “And in a clinical trial, when you see a dropout rate

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New drugs and dosage forms

**Bromfenac** ophthalmic solution (Bromday, Ista Pharmaceuticals): The product is indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.

**Lurasidone hydrochloride** tablets (Latuda, Sunovion Pharmaceuticals): The atypical antipsychotic drug is indicated for the treatment of patients with schizophrenia.

**Norethindrone acetate and ethinyl estradiol** tablets, ethinyl estradiol tablets, and **ferrous fumarate** tablets (Lo Loestrin Fe, Warner Chilcott): The combination product is indicated for use by women to prevent pregnancy.

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that’s that high, you tend to think that it’s going to be higher in the real world.”

Bhatt said he would not expect dabigatran etexilate-related dyspepsia to disappear, a consequence of the product’s formulation.

The labeling for Pradaxa capsules lists tartaric acid among the inactive ingredients. Bhatt said the inclusion of tartaric acid in the formulation means that dabigatran etexilate, a prodrug, needs an acidic environment for absorption.

**Monitoring can be a positive.** Medications that reduce gastric acid may decrease the effectiveness of dabigatran, he said.

“In this case, the lack of [blood] monitoring could be a problem,” Bhatt said, “because now you don’t know how much [drug] they’re getting and if they’re getting an effective amount of anticoagulation.”

The labeling for dabigatran etexilate recommends avoiding concomitant therapy with P-glycoprotein inducers because the latter group of drugs can reduce patients’ exposure to dabigatran.

As for P-glycoprotein inhibitors, the labeling states that dosage adjustments are not required for ketoconazole, verapamil, amiodarone, quinidine, or clarithromycin when taken concomitantly with dabigatran etexilate.

Wittkowsky said drug interactions with dabigatran will pose challenges for clinicians who work in the field of anticoagulation.

“We have always had the INR to assess how a patient is responding to an interacting agent,” she said. “And here, there is no monitoring mechanism to assess drug interactions.”

Without the need to monitor blood-test results, clinicians may neglect to educate patients on how to recognize the signs and symptoms of stroke and bleeding during therapy with dabigatran etexilate, Wittkowsky said.

“My biggest fear is that it will be used without thinking, and that that will compromise its availability long-term,” she said.

Wittkowsky is part of the faculty for an ASHP-coordinated series of educational activities on stroke prevention during atrial fibrillation. She said she has no involvement with Boehringer Ingelheim, which is supporting the series through an educational grant.

**Market potential.** Researchers several years ago predicated that 2.66 million adults in the United States will have atrial fibrillation in 2010.

The “overwhelming majority” of these patients, the researchers wrote, will not have underlying rheumatic or valvular heart disease.

Wittkowsky said about half of her anticoagulation service’s inpatients and outpatients have nonvalvular atrial fibrillation.

She predicted a “cautious and slow uptake” of dabigatran etexilate, as there was initially with low-molecular-weight heparins.

Bhatt said at least 35% of Beth Israel Deaconess inpatients receiving warfarin have nonvalvular atrial fibrillation.

For those who have been stabilized on warfarin for many years, he said, there is not a great impetus to change the anticoagulant.

Bhatt said an important consideration in starting patients on dabigatran etexilate therapy is insurers’ coverage of prescriptions for the new drug. Third-party payers may require evidence of warfarin-therapy failure or prior authorization of prescriptions for dabigatran etexilate.

“We’re going to have to know that information prior to discharge because we wouldn’t be able to ethically start somebody on that drug and then not have them have access to it at home,” he said.

—Cheryl A. Thompson

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