U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA Drug Safety Communication: FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin

This information is in follow-up to the FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran) that was issued on November 2, 2012.

Safety Announcement

[05-13-2014] In its ongoing review of the blood thinner Pradaxa (dabigatran), the U.S. Food and Drug Administration (FDA) recently completed a new study in Medicare patients comparing Pradaxa to the blood thinner warfarin (Coumadin, Jantoven, and generics), for risk of ischemic or clot-related stroke, bleeding in the brain, major gastrointestinal (GI) bleeding, myocardial infarction (MI), and death. Pradaxa and warfarin are used to reduce the risk of stroke and blood clots in patients with a common type of abnormal heart rhythm called non-valvular atrial fibrillation (AF).

The new study included information from more than 134,000 Medicare patients, 65 years or older, and found that among new users of blood-thinning drugs, Pradaxa was associated with a lower risk of clot-related strokes, bleeding in the brain, and death, than warfarin. The study also found an increased risk of major gastrointestinal bleeding with use of Pradaxa as compared to warfarin. The MI risk was similar for the two drugs.

Importantly, the new study is based on a much larger and older patient population than those used in FDA's earlier review of post-market data, and employed a more sophisticated analytical method to capture and analyze the events of concern. This study's findings, except with regard to MI, are consistent with the clinical trial results that provided the basis for Pradaxa's approval.

As a result of our latest findings, we still consider Pradaxa to have a favorable benefit to risk profile and have made no changes to the current label or recommendations for use. Patients should not stop taking Pradaxa (or warfarin) without first talking with their health care professionals. Stopping the use of blood-thinning medications such as Pradaxa and warfarin can increase the risk of stroke and lead to permanent disability and death. Health care professionals who prescribe Pradaxa should continue to follow the dosing recommendations in the drug label.

We urge both health care professionals and patients to report side effects involving Pradaxa or warfarin to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Facts about Pradaxa (dabigatran etexilate mesylate)

- From approval in October 2010 through December 2013, there were approximately 6.2 million prescriptions dispensed and 934,000 patients who received a prescription for Pradaxa® (dabigatran etexilate mesylate) from U.S. outpatient retail pharmacies.[2]

Data Summary

FDA completed an observational cohort study of Medicare beneficiaries that compared Pradaxa (dabigatran) and warfarin for rates of ischemic stroke, intracranial hemorrhage, major gastrointestinal (GI) bleeding, myocardial infarction (MI), and death. The study included new users of Pradaxa and warfarin who had received a diagnosis of atrial fibrillation (AF) in the 6 months prior to the first dispensing of medication. The study included more than 134,000 patients and 37,500 person-years of follow-up. Administrative and insurance claims data were used to identify patient outcomes.

Pradaxa was associated with:

- a lower risk of ischemic stroke, intracranial hemorrhage, and death compared to warfarin;
- an increased risk of major GI bleeding compared to warfarin; and
- a similar risk for MI compared to warfarin.

These findings, with the exception of the MI finding, are consistent with results of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial that supported FDA's approval of Pradaxa.[1] In the RE-LY study, an increased risk of MI was observed for Pradaxa compared to warfarin.

Table 1. Incidence rates and adjusted hazard ratios comparing matched new user cohorts treated with Pradaxa 75 mg or 150 mg* or warfarin for non-valvular atrial fibrillation based on 2010-2012 Medicare data. Warfarin is the reference group.

	Incidence rate per 1,000 person-years		Adjusted hazard ratio (95% CI)
	Pradaxa (dabigatran)	Warfarin	
Ischemic stroke	11.3	13.9	0.80 (0.67-0.96)
Intracranial	3.3	9.6	0.34 (0.26-0.46)

hemorrhage			
Major GI bleeding	34.2	26.5	1.28 (1.14-1.44)
Acute MI	15.7	16.9	0.92 (0.78-1.08)
Mortality	32.6	37.8	0.86 (0.77-0.96)

* Primary findings for Pradaxa are based on analysis of both 75 and 150 mg together without stratification by dose.

This study included adjustments for many potential confounding variables; however, confounding from other unmeasured factors may be present. Outcomes were largely based on previously validated algorithms with high positive predictive values but were not validated by medical record review.

The results for major GI bleeding differ from those of our previous Mini Sentinel Modular Program analysis which found lower rates of GI and intracranial hemorrhages among new users of Pradaxa, compared to new users of warfarin. Approximately 10,600 new users of Pradaxa were included in this analysis, two-thirds (64%) of whom were over age 65. The Modular Program analysis did not allow for rigorous adjustment of confounding variables as was possible with the Medicare data.

The larger Medicare study, which assessed a relatively older population (all over 65 years of age) found that Pradaxa was associated with an increased risk of major GI bleeding compared to warfarin. This finding is consistent with the RE-LY trial which showed that the risk of GI bleeding with Pradaxa compared to warfarin increased with age. The disparity between the results of the Medicare study and the prior Mini Sentinel Modular Program analysis may reflect the age differences in the two patient populations.

FDA plans to publish the study of Medicare patients. FDA also continues to investigate the reasons for differences in major GI bleeding rates for Pradaxa and warfarin observed in the Mini-Sentinel and Medicare analyses.

We are continuing to review anticoagulant use and the risk of bleeding and will communicate any relevant information that becomes available.

References

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-1151.

2. IMS, National Prescription Audit (NPA) and IMS, Vector One®: Total Patient Tracker (TPT) Databases. October 2010-December 2013. Extracted February 2014.