Drugs

FDA Drug Safety Communication: Update on the risk for serious bleeding events with the anticoagulant Pradaxa

This update is a follow-up to the FDA Drug Safety Communication of 12/7/2011[1]: Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate)

Safety Announcement

[11-02-2012] The U.S. Food and Drug Administration (FDA) has evaluated new information about the risk of serious bleeding associated with use of the anticoagulants (blood thinners) dabigatran (Pradaxa) and warfarin (Coumadin, Jantoven, and generics). Following the approval of Pradaxa, FDA received a large number of post-marketing reports of bleeding among Pradaxa users. As a result, FDA investigated the actual rates of gastrointestinal bleeding (occurring in the stomach and intestines) and intracranial hemorrhage (a type of bleeding in the brain) for new users of Pradaxa compared to new users of warfarin. This assessment was done using insurance claims and administrative data from FDA's Mini-Sentinel pilot of the Sentinel Initiative[2]. The results of this Mini-Sentinel assessment indicate that bleeding rates associated with new use of Pradaxa do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the large clinical trial used to approve Pradaxa (the RE-LY trial).[1] (see Data Summary). FDA is continuing to evaluate multiple sources of data in the ongoing safety review of this issue.

Pradaxa and warfarin are important medications used to reduce the risk of stroke and blood clots in patients with non-valvular atrial fibrillation (AF), the most common heart rhythm abnormality, which causes the heart (upper chambers or atria) to beat rapidly and irregularly. Although these drugs reduce the number of strokes in patients with non-valvular AF, they can cause bleeding, potentially leading to serious or even fatal outcomes. The risk of bleeding is a well-recognized risk of anticoagulant drugs.

FDA has not changed its recommendations regarding Pradaxa. Pradaxa provides an important health benefit when used as directed. Healthcare professionals who prescribe Pradaxa should carefully follow the dosing recommendations in the drug label, especially for patients with renal impairment (when kidneys don't function normally) to reduce the risk of bleeding. Patients with atrial fibrillation should not stop taking Pradaxa without first talking to their healthcare professional. Stopping use of anticoagulant medications such as Pradaxa can increase the risk of stroke. Strokes can lead to permanent disability and death.

Facts on Pradaxa

- Pradaxa is an anticoagulant medication used to reduce the risk of stroke and blood clots in patients with non-valvular atrial fibrillation (AF), the most common type of heart rhythm abnormality.
- The safety and efficacy of Pradaxa were studied in a clinical trial comparing Pradaxa with the anticoagulant warfarin. In the trial, patients taking Pradaxa had fewer strokes than those who took warfarin.[1]
- From approval in October 2010 through August 2012, a total of approximately 3.7 million Pradaxa prescriptions were dispensed, and approximately 725,000 patients received a dispensed prescription for Pradaxa from U.S. outpatient retail pharmacies.[2]

Mini-Sentinel is a pilot project of the Sentinel Initiative. The Sentinel Initiative is sponsored by FDA to create an active surveillance system using pre-existing electronic healthcare data from multiple sources to assess the safety of approved drugs and other medical products. See the Data Summary section for additional information on the findings, strengths and limitations of the Mini-Sentinel assessment.

As part of an ongoing safety review of Pradaxa, FDA is also conducting two planned, protocol-based observational assessments which will assess patients taking Pradaxa and evaluate bleeding events. The agency will continue to communicate to health professionals and the public any relevant information that becomes available on the risk of bleeding and Pradaxa.

Additional Information for Patients

- Pradaxa is an anticoagulant (blood-thinning) medicine that may help prevent blood clots from forming in your body and causing a stroke. Having a stroke, which is when the flow of blood to your brain is decreased or

stopped, can cause permanent disability and death.

- Do not stop taking Pradaxa without talking to your healthcare professional first. Stopping use of anticoagulants suddenly can put you at risk of a stroke.
- Be aware that while taking Pradaxa you may bruise more easily, and it may take longer for any bleeding to stop.
- Call your healthcare professional and seek immediate care if you develop any of the following signs or symptoms:
    - unusual bleeding from the gums
    - frequent nose bleeding
    - heavier-than-normal menstrual or vaginal bleeding during your periods
    - severe bleeding or bleeding you cannot control
    - pink or brown urine
    - red or black stools (may look like tar)
    - bruises that happen or get larger without a known cause
    - coughing up blood or blood clots
    - vomiting blood or vomit that looks like coffee grounds
- Discuss any questions or concerns about Pradaxa with your healthcare professional.
- Report any side effects you experience to your healthcare professional and the FDA MedWatch program using the information in the “Contact Us” box at the bottom of the page.

Additional Information for Healthcare Professionals (updated from 12/7/2011)

- Results from the FDA assessment of bleeding rates using data from the Mini-Sentinel project indicate that intracranial and gastrointestinal hemorrhage incidence rates for new users of Pradaxa do not appear to be higher than the rates for the same types of bleeding for new users of warfarin.
- Make sure your patients know the signs and symptoms of bleeding and when to seek care.
- Pradaxa is approved to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
- Pradaxa is eliminated by the kidneys, therefore:
    - Renal function should be assessed prior to treatment with Pradaxa to determine the appropriate dose.
    - Renal function should be reassessed during treatment with Pradaxa if clinically indicated (e.g., fluctuating renal function, diuretic use, hypovolemia), and the dose should be adjusted following the recommendations in the drug label.
- For patients with creatinine clearance (CrCl) > 30 mL/min, the recommended dose of Pradaxa is 150 mg given orally twice daily.
- For patients with severe renal impairment, follow the recommended doses:
    - For patients with CrCl 15-30 mL/min, the recommended dose is 75 mg orally twice daily.
    - Dosing recommendations for patients with a CrCl <15 mL/min or on dialysis cannot be provided.
- Report adverse events involving Pradaxa to the FDA MedWatch program using the information in the “Contact Us” box at the bottom of the page.

Data Summary

Pradaxa (dabigatran) and warfarin are important medications used to reduce the risk of stroke and blood clots in patients with non-valvular atrial fibrillation. Bleeding that may lead to serious or even fatal outcomes is a well-recognized complication of all anticoagulant therapies. In the large clinical trial with 18,000 patients that compared the efficacy and safety of Pradaxa and warfarin (RE-LY, 2010), the rate of serious bleeding was similar between the two drugs.[1] However, after Pradaxa’s approval, a large number of reports of bleeding were submitted to FDA’s Adverse Events Reporting System (AERS) database.

FDA believes that a simple comparison between Pradaxa and warfarin with respect to the numbers of post-marketing reports of bleeding in the AERS database is misleading because bleeding events associated with warfarin (a well-recognized consequence of warfarin use, which has been available for many years) are likely underreported compared to events occurring with the more recently available Pradaxa. [See DSC from 12/7/11[3] for further discussion] FDA continues to evaluate multiple sources of data in the ongoing safety review of this issue.

Mini-Sentinel Database Assessment

To compare rates of certain bleeding events in patients receiving Pradaxa or warfarin, FDA assessed the actual rates of gastrointestinal and intracranial hemorrhage using health insurance claims and administrative data from FDA’s

Mini-Sentinel pilot of the Sentinel Initiative[4].

The population upon which the Mini-Sentinel data are based is not necessarily representative of the general U.S. population, but it can provide information on a defined patient population. The Mini Sentinel population provides both the number of events and the number of patients, which allows calculation of incidence rates (the number of new cases of a disease or condition occurring in a population during a certain time period).

The Mini-Sentinel database was queried to identify inpatient diagnosis codes for intracranial and gastrointestinal hemorrhage events (ICH and GIH, combined and separately) associated with new use of Pradaxa or warfarin during the time period from October 19, 2010 (FDA approval date of Pradaxa), through December 31, 2011. Individuals were included in this assessment if they: 1) were enrolled in a participating health plan with both drug and medical coverage for a period of 6 months prior to their first being dispensed either drug; and 2) they had a diagnosis code for atrial fibrillation during this 6-month period; and 3) they did not receive either anticoagulant or a diagnosis code for GIH or ICH during this 6-month period. Additional analyses were conducted wherein these three criteria were relaxed to include as many Pradaxa users as possible in the same time interval under evaluation. Similar results were obtained from all analyses.

For the populations in the Mini-Sentinel data assessment, the combined incidence rate (ICH and GIH events per 100,000 days at risk) was 1.8 to 2.6 times higher for new users of warfarin than for new users of Pradaxa. The incidence rate of GIH events only per 100,000 days at risk was 1.6 to 2.2 times higher for warfarin new users than for Pradaxa new users, and the incidence rate of ICH events only per 100,000 days at risk was 2.1 to 3.0 times higher with warfarin than with Pradaxa. The results indicate that the observed bleeding rates associated with new use of Pradaxa do not appear to be higher than the bleeding rates associated with new use of warfarin.

The estimates do not account for possible differences in the patient populations for the two drugs that may relate to bleeding outcomes, such as age and the presence of other medical conditions. It is also not known whether the codes for ICH, GIH, and atrial fibrillation actually reflect the existence of those conditions in patients using anticoagulants; such information can only be gained through detailed review of medical records.

As part of its ongoing safety review of Pradaxa, FDA is conducting two additional protocol-based observational assessments using Mini Sentinel data. In addition, FDA continues to monitor post-market reports for evidence of inappropriate dosing, use of interacting drugs, and other clinical factors that might lead to a bleeding event and will communicate any relevant information on the risk of bleeding and Pradaxa.

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, Vector One®: National (VONA) and Total Patient Tracker (TPT) Database. October 2010 to August 2012. Extracted September 2012.

Related Information

- FDA Drug Safety Communication: Safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate)[5]
- Information on Dabigatran Etexilate Mesylate (marketed as Pradaxa)[6]

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Mail to: MedWatch 5600 Fishers Lane
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