FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug

Safety Announcement

[03-12-2010] The U.S. Food and Drug Administration (FDA) has added a Boxed Warning to the label for Plavix, the anti-blood clotting medication. The Boxed Warning is about patients who do not effectively metabolize the drug (i.e. "poor metabolizers") and therefore may not receive the full benefits of the drug.

The Boxed Warning in the drug label will include information to:

- Warn about reduced effectiveness in patients who are poor metabolizers of Plavix. Poor metabolizers do not effectively convert Plavix to its active form in the body.
- Inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function.
- Advise healthcare professionals to consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.

Plavix is given to reduce the risk of heart attack, unstable angina, stroke, and cardiovascular death in patients with cardiovascular disease. Plavix works by decreasing the activity of blood cells called platelets, making platelets less likely to form blood clots.

For Plavix to work, enzymes in the liver (particularly CYP2C19) must convert (metabolize) the drug to its active form. Patients who are poor metabolizers of the drug, do not effectively convert Plavix to its active form. In these patients, Plavix has less effect on platelets, and therefore less ability to prevent heart attack, stroke, and cardiovascular death. It is estimated that 2 to 14% of the population are poor metabolizers; the rate varies based on racial background.

Healthcare professionals should be aware that a subgroup of patients are poor metabolizers and do not metabolize Plavix effectively; this can result in reduced effectiveness of Plavix. Healthcare professionals should consider use of other anti-platelet medications or alternative dosing strategies for Plavix in these patients.

Patients should not stop taking Plavix unless told to do so by their healthcare professional. They should talk with their healthcare professional if they have any concerns about Plavix, or to find out if they should be tested for being a poor metabolizer.

In May 2009, FDA added information about poor metabolizers of Plavix to the drug label. However, based on additional data reviewed by the agency (see Data Summary below) the Boxed Warning is now being added to highlight the reduced effectiveness of Plavix in these patients and to recommend that healthcare professionals consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.

Additional Information for Patients
Patients currently taking Plavix should:

- Be aware that some patients do not convert Plavix to its active form as well as other patients. These patients may not get the same benefit from Plavix and are known as poor metabolizers.
- Not stop taking Plavix unless told to do so by their healthcare professional.
- Talk with their healthcare professional if they have any concerns about Plavix.
- Talk with their healthcare professional to see if testing to determine their metabolizer status is appropriate.

Additional Information for Healthcare Professionals

FDA recommends that healthcare professionals should:

- Be aware that some patients may be poor metabolizers of Plavix. They do not effectively convert Plavix to its active form because of low CYP 2C19 activity. The effectiveness of Plavix as a preventive therapy is reduced in these patients.
- Be aware that tests are available to determine patients' CYP2C19 status.
- Consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients who have been identified as poor metabolizers.
- Be aware that although a higher dose regimen (600 mg loading dose followed by 150 mg once daily) in poor metabolizers increases antiplatelet response, an appropriate dose regimen for poor metabolizers has not been established in a clinical outcome trial.
- Review the newly approved Plavix drug label for complete information on the use of Plavix.

Data Summary

The liver enzyme CYP2C19 is primarily responsible for the formation of the active metabolite of Plavix. Pharmacokinetic and antiplatelet tests of the active metabolite of Plavix show that the drug levels and antiplatelet effects differ depending on the genotype of the CYP2C19 enzyme. The following represent the different alleles of CYP2C19 that make up a patient's genotype:

- The CYP2C19*1 allele has fully functional metabolism of Plavix.
- The CYP2C19*2 and *3 alleles have no functional metabolism of Plavix. These two alleles account for most of the reduced function alleles in patients of Caucasian (85%) and Asian (99%) descent classified as poor metabolizers.
- The CYP2C19*4, *5, *6, *7, and *8 and other alleles may be associated with absent or reduced metabolism of Plavix, but are less frequent than the CYP2C19*2 and *3 alleles.
- A patient with two loss-of-function alleles (as defined above) will have poor metabolizer status.

The pharmacokinetic and antiplatelet responses to Plavix were evaluated in a crossover trial in 40 healthy subjects. Ten subjects in each of the four CYP2C19 metabolizer groups (ultrarapid, extensive, intermediate and poor) were randomized to two treatment regimens: a 300 mg loading dose followed by 75 mg per day, or a 600 mg loading dose followed by 150 mg per day, each for a total of 5 days. After a washout period, subjects were crossed over to the alternate treatment. Decreased active metabolite exposure and decreased platelet aggregation were observed in the poor metabolizers compared to the other groups. When poor metabolizers received the 600 mg loading dose followed by 150 mg daily, active metabolite exposure and antiplatelet response were greater than with the 300 mg/75 mg regimen. Healthcare professionals should note that an appropriate dose regimen for patients who are poor metabolizers has not been established in clinical outcome trials.