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VETERANS HEALTH ADMINISTRATION (VHA) PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), & CENTER FOR MEDICATION SAFETY (VA MEDSAFE)

CLOPIDOGREL AND BOXED WARNING REGARDING POOR METABOLIZERS

I. ISSUE

On March 12, 2010, the FDA updated the product labeling for clopidogrel to contain a boxed warning regarding the following issues:

- Clopidogrel can be less effective in people who cannot metabolize the drug and convert it to its active form.
- Genetic testing can identify differences in patients' metabolic function by the 2C19 enzyme system.
- In patients tested and confirmed as poor metabolizers, consider other anti-platelet agents or use alternate clopidogrel dosing strategies.

II. BACKGROUND

Clopidogrel is a prodrug that requires biotransformation via the hepatic cytochrome P450 (CYP) enzyme system to the active compound. Genetic polymorphisms, particularly in the alleles that comprise the CYP2C19 enzyme, may alter metabolism of clopidogrel, decreasing its activity. Poor metabolizers of clopidogrel exist in approximately 3% of the general population and vary by ethnicity, affecting 4% of African Americans and 14% of Chinese.

The new boxed warning resulted after FDA reviewed an industry-sponsored crossover trial in 40 healthy subjects that looked at how four CYP2C19 metabolizer groups (ultrarapid, extensive, intermediate and poor) responded to two clopidogrel treatments (with a washout in between): either 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. Results showed decreased active metabolite exposure and decreased inhibition of platelet aggregation in the poor metabolizer group 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. These results have not been correlated to any clinical outcomes.

Currently, there is a single test approved by the FDA to identify 2C19 genetic differences. Roche's ***AmpliChip*** , is a pharmacogenetic test for analysis of the CYP2D6 and CYP2C19 genes. The test has not been given an FDA approved indication for monitoring and adjusting dosing of clopidogrel therapy.

Clopidogrel is used in both acute and elective settings. The 2C19 genetic testing varies among laboratories and may require hours to weeks to receive a final result. This may not appropriate in the setting of ACS or emergent stenting.

III. SUMMARY and PROVIDER RECOMMENDATIONS

- A subpopulation of patients who are treated with clopidogrel may be poor metabolizers of the drug and may demonstrate a decreased antiplatelet response.
- There is inadequate evidence for routine genetic testing for CYP 2C19 abnormalities in patients requiring antiplatelet therapy. Likewise, there is inadequate evidence to inform the most appropriate treatment in those patients with genetic polymorphisms. Therefore, until definitive evidence becomes available, the decision to do CYP2C19 testing (and any subsequent treatment decisions based on results of testing) may be considered on a case by case basis.
- If hypometabolism is suspected, a platelet aggregation study while on medication is an alternative testing option.
- There is only one FDA-approved test for identification of genetic mutation of the 2C19 enzyme.
- FDA offers two options for poor metabolizers in the black box warning. It advises health care professionals to consider using other anti-platelet medications or alternative dosing strategies.
- The FDA notes that although the use of alternate clopidogrel dosing regimens (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. This dosing schedule is not an FDA-approved regimen.

IV. REFERENCES

1. Food and Drug Administration. FDA drug safety communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug [safety announcement]. March 12, 2010. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm

2. Sanofi-Aventis and Bristol-Myers Squibb announce important updates to PLAVIX US prescribing information [press release]. March 12, 2010. http://www.bms.com/news/press_releases/pages/default.aspx?RSSLink=http://www.businesswire.com/news/bms/20100312005836/en&t=634045283354837137

ACTIONS:

- ***Facility Director*** *(or physician designee): Forward this document to the Facility Chief of Staff (COS).*
- ***Facility COS and Chief Nurse Executives:*** *Forward this document to all appropriate providers who prescribe these medications (e.g.,* ***primary care providers, cardiology, and neurology****, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.*
- ***ACOS for R&D:*** *Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).*