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Clopidogrel and Alteration of Effectiveness Due to CYP2C19 Inhibitors (E.g. PPIs)

- The FDA is aware of published reports that clopidogrel is less effective in some patients than in others.¹ These differences may be attributable to 1) genetic factors linked with decreased metabolic activity (CYP3A5 and CYP2C19); and 2) potential drug interactions when prescribed concomitantly with drugs that inhibit CYP2C19.
- Clopidogrel is a prodrug that must be metabolized in the liver by CYP3A and CYP2C19 to its active form in order to inhibit adenosine diphosphate-induced platelet aggregation.
- CYP2C19 inhibitors such as proton pump inhibitors (PPIs) are often prescribed concomitantly with clopidogrel to reduce GI irritation and ulceration. PPIs include prescription omeprazole (Prilosec, Zegerid), lansoprazole (Prevacid), pantoprazole (Protonix), rabeprazole (Aciphex), and esomeprazole (Nexium), and non-prescription omeprazole (Prilosec OTC).
- Studies evaluating whether PPIs alter the ability of clopidogrel to prevent cardiovascular events have conflicting conclusions.^{2,3,4} The FDA, Sanofi-Aventis, and Bristol Myers Squibb are developing studies to investigate this association.
- It is unknown if other acid-reducers such as H₂-blockers or antacids interfere with the antiplatelet activity of clopidogrel.
- The American College of Cardiology (ACC)/American College of Gastroenterology (ACG)/American Heart Association (AHA) advise that patients on these medications not change their drug regimen unless advised by their healthcare provider.⁵
- FDA recommends the following:
 - Healthcare providers should continue to prescribe and patients should continue to take clopidogrel as directed, because clopidogrel has demonstrated benefits in preventing blood clots that could lead to a heart attack or stroke.
 - Healthcare providers should re-evaluate the need for starting or continuing treatment with a PPI, including Prilosec OTC, in patients taking clopidogrel.
 - Patients taking clopidogrel should consult with their healthcare provider if they are currently taking or considering taking a PPI, including Prilosec OTC.
- PBM/VAMedSAFE acknowledges that there is no definitive evidence that the use of PPIs decreases the effectiveness of clopidogrel, although the potential for this interaction is a serious concern. VAMedSAFE continues to evaluate outcomes of patients on concomitant clopidogrel and PPI therapy. This FDA communication does not change PBM's recommendations for appropriate use of clopidogrel; use of a concomitant PPI should be assessed in light of the emerging data.

REFERENCES

1. FDA. http://www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm. (Accessed January 28, 2009)
2. Siller-Matula JM et al. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. Am Heart J. 2009 Jan;157(1):148.e1-5.
3. Gilard M et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole Clopidogrel Aspirin) study. J Am Coll Cardiol. 2008 Jan 22;51(3):256-60.
4. Gurbel PA et al. Omeprazole: a possible new candidate influencing the antiplatelet effect of clopidogrel. J Am Coll Cardiol. 2008 Jan 22;51(3):261-3.
5. <http://www.acc.org/media/releases/highlights/2008/nov08/ppi.htm> Online Accessed 11-12-08.

ACTIONS

- **Facility COS:** Forward this document to all appropriate providers who prescribe these medications (e.g., **primary care providers, cardiology and GI specialists**, 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).