Early Communication about an Ongoing Safety Review of clopidogrel bisulfate (marketed as Plavix)

This information reflects FDA's current analysis of available data concerning these drugs. Posting this information does not mean that FDA has concluded there is a cause and effect relationship between the drug products and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing these products. FDA is considering, but has not reached a conclusion about whether this information warrants any regulatory action. FDA intends to update this document when additional information or analyse become available

The FDA is aware of published reports that clopidogrel (marketed as Plavix) is less effective in some patients than it is in others. Differences in effectiveness may be due to genetic differences in the way the body metabolizes clopidogrel,[1, 2] or that using certain other drugs with clopidogre can interfere with how the body metabolizes clopidogrel.[3]

Clopidogrel is an antiplatelet drug that is used to prevent blood clots that could lead to heart attacks or strokes in patients at risk for these problems. The drug clopidogrel is a "pro-drug" which means that it has to be metabolized by the body before it can be biologically active and have the effect of preventing blood clots. Understanding that there are differences in how the body metabolizes clopidogrel and there are effects that other drugs may have on its metabolism i important because decreases in the effectiveness of clopidogrel might be avoided, in part, by using other drugs with clopidogrel that do not interfere with its metabolism.

One class of drugs commonly used with clopidogrel is proton pump inhibitors (PPIs). Some reports suggest that use of certain PPIs may make clopidogrel less effective[3, 4] by inhibiting the enzyme that converts clopidogrel to the active form of the drug. Other reports do not suggest thi effect.[5, 6] Proton pump inhibitors decrease stomach acid and are used to treat frequent heartburn and stomach ulcers. Clopidogrel can irritate the stomach so PPIs are commonly used with clopidogrel to help reduce this irritation. PPIs include omeprazole (Prilosec, Zegerid), lansoprazole (Prevacid), pantoprazole (Protonix), rabeprazole (Aciphex), and esomeprazole (Nexium), which are all available by prescription. Omeprazole (Prilosec OTC) is also sold without a prescription (over-the-counter) for frequent heartburn.

Currently, we have no evidence that other drugs that reduce stomach acid, such as H2 blockers (e.g., Zantac, Pepcid, Tagamet and Axid) or antacids interfere with the antiplatelet activity of clopidogrel.

The makers of Plavix, Sanofi-Aventis and Bristol-Myers Squibb, have agreed to work with FDA

to conduct studies to obtain additional information that will allow us to better understand and characterize the effects of genetic factors and other drugs (especially the PPIs) on the effectiveness of clopidogrel. This information should lead to a better understanding about how to optimize the use of clopidogrel. The FDA recognizes the importance of obtaining these data promptly. The drug manufacturers have agreed to a timeline for completing the studies. The FDA will review the new information expeditiously upon receipt from the drug manufacturers and will communicate its conclusions and any recommendations to the public at that time. It could take several months to complete the studies and analyze the results.

Until further information is available 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 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.

This early communication is in keeping with FDA's commitment to inform the public about its ongoing safety reviews of drugs.

The FDA urges both healthcare professionals and patients to report side effects from the use of clopidogrel to the FDA's MedWatch Adverse Event Reporting program

- online at www.fda.gov/medwatch/report.htm;
- by returning the postage-paid FDA form 3500 available in PDF format at www.fda.gov/medwatch/getforms.htm to 5600 Fishers Lane, Rockville, MD 20852-9787;
- faxing the form to 1-800-FDA-0178; or
- by phone at 1-800-332-1088

[1] Frere C et al, Effect of cytochrome P450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. Am J Cardiol 2008; 101:1088-93.

[2] Trenk et al. Cytochrome P450 2C19 681G A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug eluting or bare-metal stents. J Am Coll Cardiol 2008; 51: 1925-34.

[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: 51:256-60.

[4] Gilard M et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated to aspirin. J Thromb Haemost 2006; 4:2508-9.

[5] Small DS et al. Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel. J Clin Pharmacol 2008; 48: 475-484.

[6] Siller-Matula JM et al. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. Am Heart J 2009; 157:148e1-148.e5.

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