June 19th 2013

Regarding Bleeding Risk with Plavix (Clopidogrel 75mg) in Atrial Fibrillation Patients

Dear Healthcare Professional:

The Saudi Food and Drug Authority (SFDA) has approved extending Plavix indication to include:
"Prevention of atherothrombotic and thromboembolic events including stroke in adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk, clopidogrel is indicated in combination with acetylsalicylic acid ASA"

In patients with atrial fibrillation (AF) at increased risk of vascular events who can take VKA therapy, VKA has been shown to be associated with a better clinical benefit than (ASA) alone or the combination of clopidogrel and ASA for the reduction of stroke.

In patients with atrial fibrillation who have at least one risk factor for vascular events and who cannot take VKA therapy (e.g., specific risk of bleeding, physician assessment that patient is unable to comply with INR (international normalised ratio) monitoring or that VKA use is inappropriate), clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke. Clopidogrel in combination with ASA has been shown to reduce the rate of the combined endpoint of stroke, myocardial infarction (MI), non-CNS systemic embolism, or vascular death, largely through a reduction in stroke.

This new indication for clopidogrel in the frame of the labelling indication was granted and approved based on ACTIVE-W[1] and ACTIVE-A[2] studies' results. The recommended dose should be given as a single daily dose of clopidogrel 75 mg and ASA (75-100 mg daily) should be initiated and continued in combination with clopidogrel.

Bleeding Risk:

Bleeding is the most common reaction reported both in clinical studies as well as in post-marketing experience, where it was mostly reported during the first month of treatment.

In ACTIVE-A, the rate of major bleeding was greater in the clopidogrel + ASA group than in the placebo + ASA group (6.7% versus 4.3%). Major bleeding was mostly of extra cranial origin in both groups (5.3% in the clopidogrel + ASA group; 3.5% in the placebo +ASA group), mainly from the gastrointestinal tract (3.5% vs. 1.8%). There was an excess of intracranial bleeding in the clopidogrel + ASA treatment group compared to the placebo + ASA group (1.4% versus 0.8%, respectively). There was no statistically significant difference in the rates of fatal bleeding (1.1% in the clopidogrel + ASA group and 0.7% in the placebo +ASA group) and haemorrhagic stroke (0.8% and 0.6%, respectively) between groups.

ACTIVE Program:

The ACTIVE-W[1] and ACTIVE-A[2] studies, separate trials in the ACTIVE program, included patients with atrial fibrillation (AF) who had at least one risk factor for vascular events. Based on enrolment criteria, physicians enrolled patients in ACTIVE-W if they were candidates for vitamin K antagonist (VKA) therapy (such as warfarin). The ACTIVE-A study included patients who could not receive VKA therapy because they were unable or unwilling to receive the treatment.

The ACTIVE-W study demonstrated that **anticoagulant treatment with vitamin K antagonists was more effective than with clopidogrel and ASA.**

The ACTIVE-A study (N=7,554) was a multicentre, randomized, double-blind, placebo-controlled study which compared clopidogrel 75 mg/day + ASA (N=3,772) to placebo + ASA (N=3,782). The recommended dose for ASA was 75 to 100 mg/day. Patients were treated for up to 5 years.

Patients randomized in the ACTIVE program were those presenting with documented AF, i.e., either permanent AF or at least 2 episodes of intermittent AF in the past 6 months, and had at least one of the following risk factors: age ≥75 years or age 55 to 74 years and either diabetes mellitus requiring drug therapy, or documented previous MI or documented coronary artery disease; treated for systemic hypertension; prior stroke, transient ischaemic attack (TIA), or non-CNS systemic embolus; left ventricular dysfunction with left ventricular ejection fraction <45%; or documented peripheral vascular disease. The mean $CHADS_2$ score was 2.0 (range 0-6).

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The major exclusion criteria for patients were documented peptic ulcer disease within the previous 6 months; prior intracerebral haemorrhage; significant thrombocytopenia (platelet count < 50 x 10^9/l); requirement for clopidogrel or oral anticoagulants (OAC); or intolerance to any of the two compounds.

Seventy-three percent (73%) of patients enrolled into the ACTIVE-A study were unable to take VKA due to physician assessment, inability to comply with INR (international normalised ratio) monitoring, predisposition to falling or head trauma, or specific risk of bleeding; for 26% of the patients, the physician's decision was based on the patient's unwillingness to take VKA.
The patient population included 41.8 % women. The mean age was 71 years, 41.6% of patients were ≥75 years. A total of 23.0% of patients received anti-arrhythmics, 52.1% beta-blockers, 54.6% ACE inhibitors, and 25.4% statins.

The number of patients who reached the primary endpoint (time to first occurrence of stroke, MI, non-CNS systemic embolism or vascular death) was 832 (22.1%) in the group treated with clopidogrel + ASA and 924 (24.4%) in the placebo + ASA group (relative risk reduction of 11.1%; 95% CI of 2.4% to 19.1%; p=0.013), primarily due to a large reduction in the incidence of strokes. Strokes occurred in 296 (7.8%) patients receiving clopidogrel + ASA and 408 (10.8%) patients receiving placebo + ASA (relative risk reduction, 28.4%; 95% CI, 16.8% to 38.3%; p=0.00001).

This letter is sent in agreement with the Saudi Food and Drug Authority

Call for Reporting:

Patient safety is the highest priority for Sanofi and we are committed to ensuring that healthcare professionals continue to have the information necessary to prescribe Plavix® appropriately. Please review carefully the enclosed and contact SANOFI if you have any additional questions.

Any suspected adverse events experienced by your patients should be reported to the national Pharmacovigilance centre in Saudi Arabia.

Saudi Food and Drug Authority
National Pharmacovigilance and Drug Safety Center
Fax: +966-11-2057662
E-Mail: npc.drug@sfda.gov.sa

In addition, suspected adverse reactions related to SANOFI products may be reported to SANOFI Pharmacovigilance department:

Email: KSA_Pharmacovigilance@sanofi.com
Contact person: Dr Mohamed El-Tawwab
Tel: +966-11-4633190 Ext 1147
Mobile: +966 564095175/ +966 564095014

We remain at your disposal for any further information you may need.

Yours sincerely,

Mohamed A. Moneim, MD, MSc
Director Medical Affairs

SANOFI
Saudi Arabia
Attachements:
PIL (Medication Guide) approved in Saudi Arabia in September 9th, 2012

References:

1. The ACTIVE Writing Group on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006; 367: 1903–12
2. Connolly SJ et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med. 2009 May 14;360(20):2066-78