



## **Sanofi-aventis and Bristol-Myers Squibb Announce Important Updates to PLAVIX® U.S. Prescribing Information**

(Bridgewater, NJ and Princeton, NJ, March 12, 2010) -- [Sanofi-aventis](#) U.S. and [Bristol-Myers Squibb Company](#) (NYSE: BMY) today announced revisions to the U.S. prescribing information for [PLAVIX®](#) (clopidogrel bisulfate), which include a boxed warning. The boxed warning concerns the diminished effectiveness of PLAVIX in patients who have a genetic variation leading to reduced formation of the active metabolite. These patients, who are designated as poor metabolizers, represent, according to the prescribing information, approximately 2% of whites, 4% of blacks, and 14% of Chinese. The percentage of poor metabolizers is estimated to be approximately 3% of the population, based on published studies.

Patients should continue taking PLAVIX unless told to do otherwise by their healthcare professional. They should talk with their healthcare professional if they have any concerns about PLAVIX.

Today, the U.S. Food and Drug Administration (FDA) issued a press release on this update, which is included below:

### ***FDA Announces New Boxed Warning on Plavix***

*The U.S. Food and Drug Administration today added a boxed warning to the anti-blood clotting drug Plavix (clopidogrel), alerting patients and health care professionals that the drug can be less effective in people who cannot metabolize the drug to convert it to its active form.*

*Plavix reduces the risk of heart attack, unstable angina, stroke, and cardiovascular death in patients with cardiovascular disease by making platelets less likely to form blood clots. Plavix does not have its anti-platelet effects until it is metabolized into its active form by the liver enzyme, CYP2C19.*

*People who have reduced functioning of their CYP2C19 liver enzyme cannot effectively convert Plavix to its active form. As a result, Plavix may be less effective in altering platelet activity in those people. These "poor metabolizers" may not receive the full benefit of Plavix treatment and may remain at risk for heart attack, stroke, and cardiovascular death.*

*"We want to highlight this warning to make sure health care professionals use the best information possible to treat their patients," said Mary Ross Southworth, Pharm.D., a clinical analyst in the Division of Cardiovascular and Renal Products in the FDA's Center for Drug Evaluation and Research.*

*In May 2009, the FDA added this warning to the drug's label. After reviewing more data, the agency felt it was important to highlight this risk in a boxed warning.*

*It is estimated that 2 percent to 14 percent of the U.S. population are poor metabolizers. The FDA recommends that health care professionals consider alternative dosing of Plavix for these patients, or consider using other anti-platelet medications. Tests are available to assess CYP2C19 genotype to determine if a patient is a poor metabolizer.*

*Patients should not stop taking Plavix unless told to do so by their health care professional. They should talk with their health care professional if they have any concerns about Plavix.*

*Plavix is made under a Bristol-Myers Squibb - Sanofi Pharmaceuticals partnership.*

These revisions to the prescribing information for PLAVIX<sup>®</sup> (clopidogrel bisulfate) reflect the companies' ongoing research in collaboration with the FDA, which better defines the patient population that may be affected by a genetic variation in CYP2C19 and alternate treatment strategies.

## **IMPORTANT SAFETY INFORMATION**

### **WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS**

**The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1)]. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19**

**function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy [see Clinical Pharmacology (12.5)]. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers [see Dosage and Administration (2.3)].**

### **CONTRAINDICATIONS**

Plavix is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

Plavix is contraindicated in patients with hypersensitivity (e.g., anaphylaxis) to clopidogrel or any component of the product.

### **WARNINGS AND PRECAUTIONS**

Avoid concomitant use of Plavix and drugs that inhibit CYP2C19 activity.

Co-administration of Plavix with omeprazole, a proton pump inhibitor that is an inhibitor of CYP2C19, reduces the pharmacological activity of Plavix if given concomitantly or if given 12 hours apart [see Drug Interactions (7.1)].

Thienopyridines, including Plavix, increase the risk of bleeding. If a patient is to undergo surgery and an antiplatelet effect is not desired, discontinue Plavix 5 days prior to surgery.

Avoid lapses in therapy, and if Plavix must be temporarily discontinued, restart as soon as possible. Premature discontinuation of Plavix may increase the risk of cardiovascular events.

In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and Plavix has not been shown to be more effective than Plavix alone, but the combination has been shown to increase major bleeding.

TTP, sometimes fatal, has been reported following use of Plavix, sometimes after a short exposure (<2 weeks). TTP is a serious condition that requires urgent treatment including plasmapheresis (plasma exchange).

### **ADVERSE REACTIONS**

Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction.

### **DRUG INTERACTIONS**

Coadministering warfarin with Plavix increases the risk of bleeding.

Coadministration of Plavix and NSAIDs increases the risk of gastrointestinal bleeding.

### **USE IN SPECIFIC POPULATIONS**

Nursing mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother.

## INDICATIONS

### **Acute Coronary Syndrome (ACS)**

For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)], including patients who are to be managed medically and those who are to be managed with coronary revascularization, Plavix has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

For patients with ST-elevation myocardial infarction (STEMI), Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary percutaneous coronary intervention is unknown.

The optimal duration of Plavix therapy in ACS is unknown.

### **Recent MI, Recent Stroke, or Established Peripheral Arterial Disease**

For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, Plavix has been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

**Please see full prescribing information, including BOXED WARNING** for the United States by visiting [www.PLAVIX.com](http://www.PLAVIX.com).

### **About sanofi-aventis**

Sanofi-aventis U.S. is an affiliate of sanofi-aventis, a leading global pharmaceutical company that discovers, develops and distributes therapeutic solutions to help improve the lives of patients. Sanofi-aventis is listed in Paris (EURONEXT: SAN) and in New York (NYSE:SNY) . For more information, [www.sanofi-aventis.us](http://www.sanofi-aventis.us) or [www.sanofi-aventis.com](http://www.sanofi-aventis.com).

### **About Bristol-Myers Squibb**

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information, please visit [www.bms.com](http://www.bms.com).

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**Sanofi-aventis Forward-Looking Statement**

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts. These statements include projections and estimates and their underlying assumptions, statements regarding plans, objectives, intentions and expectations with respect to future financial results, events, operations, services, product development and potential and statements regarding future performance. Forward-looking statements are generally identified by the words “expects,” “anticipates,” “believes,” “intends,” “estimates,” “plans” and similar expressions. Although sanofi-aventis’ management believes that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of sanofi-aventis, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include among other things, the uncertainties inherent in research and development, future clinical data and analysis, including post marketing, decisions by regulatory authorities, such as the FDA or the EMA, regarding whether and when to approve any drug, device or biological application that may be filed for any such product candidates as well as their decisions regarding labelling and other matters that could affect the availability or commercial potential of such products candidates, the absence of guarantee that the products candidates if approved will be commercially successful, the future approval and commercial success of therapeutic alternatives, the Group’s ability to benefit from external growth opportunities as well as those discussed or identified in the public filings with the SEC and the AMF made by sanofi-aventis, including those listed under “Risk Factors” and “Cautionary Statement Regarding Forward-Looking Statements” in sanofi-aventis’ annual report on Form 20-F for the year ended December

31, 2008. Other than as required by applicable law, sanofi-aventis does not undertake any obligation to update or revise any forward-looking information or statements.

### **Bristol-Myers Squibb Forward-looking Statement**

This press release contains “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995, regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Forward-looking statements in the press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2009, its Quarterly Reports on Form 10-Q, and Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise.

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