



Daiichi Sankyo/Lilly Respond to ACCF/AHA Clinical Alert on Antiplatelet Therapy

INDIANAPOLIS and PARSIPPANY, N.J., June 28, 2010 /PRNewswire via COMTEX News Network/ -- Daiichi Sankyo, Inc. and Eli Lilly and Company appreciate the availability of a "Clinical Alert" from the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) in response to the FDA's Boxed Warning about Plavix(R) (clopidogrel), and commend the leading cardiovascular medical societies for providing perspective on the importance of genetic make-up and the variability in response of certain oral anti-platelet (OAP) therapy for patients with acute coronary syndrome (ACS) who are managed with angioplasty and stenting (known as PCI). This statement is being issued in light of references in the Clinical Alert to the companies' co-developed product, Effient(R) (prasugrel).

"We believe the medical community will find the clinical alert from the leading cardiovascular medical societies on this important issue both timely and welcome," said LeRoy LeNarz, MD, senior medical director, Cardiovascular, Lilly USA, LLC. "It is important for physicians - and patients - to recognize the potential impact of a variety of factors, including genetics, on clopidogrel response, as well as the prevalence of these genetic variations in the general population, and we look forward to working with physicians as they identify ways to help manage these issues while the science continues to evolve."

Common Genetic Variations: No Impact on Effient

Unlike clopidogrel, there is no relevant effect of genetic variation in CYP2C19 on the pharmacokinetics of the active metabolite of Effient or its inhibition of platelet aggregation. Genetic variation in CYP2B6, CYP2C9 or CYP3A5 also has no impact on its active metabolite or inhibition of platelet aggregation.

The clopidogrel boxed warning states that patients considered "poor metabolizers" (those with two copies of the CYP2C19 variant) may have an increased risk of thrombotic cardiovascular (CV) events. In addition, the label also notes that some patients with at least one reduced-function allele (copy) of CYP2C19 (also known as intermediate metabolizers) may also have a reduced response to clopidogrel. The prevalence of poor metabolizers is estimated at 2 percent for Caucasians, 4 percent for Blacks, and 14 percent for Chinese. The prevalence of intermediate metabolizers is 28 percent for Caucasians, 33 percent for Blacks and 64 percent for Chinese.

In addition, the ACCF/AHA Clinical Alert suggests genetic variations in other genes, such as ABCB1, may also contribute to variability in response to clopidogrel. A retrospective analysis of the TRITON-TIMI 38 trial suggested that patients treated with Effient with two variants in ABCB1 did not have an increased risk of thrombotic CV events when compared to patients treated with Effient without these variants.

"The ability to convert Effient to its active metabolite is not known to be impacted by the key genetic variations discussed in the Clinical Alert," said Rogelio Braceras, MD, senior medical director, thrombosis at Daiichi Sankyo, Inc. "In addition, other high-risk patient types mentioned in the Clinical Alert, such as those with diabetes or those who are more susceptible to recurrent events, such as STEMI patients, achieved reductions in the primary composite endpoint of CV death, nonfatal heart attack or nonfatal stroke in TRITON-TIMI 38 that were consistent with those observed in the UA/NSTEMI cohort and the overall all ACS population. This benefit, however, should be weighed against the potential risk of clinically significant bleeding, which in TRITON-TIMI 38 was significantly higher with Effient when compared with clopidogrel."

As pointed out in the Clinical Alert, research has shown other factors beyond genetics can negatively impact response to clopidogrel in some ACS-PCI patients. These factors include diabetes status, heart attack severity, stent type and concomitant medications.

In TRITON-TIMI 38, Effient produced reductions in the primary composite endpoint of CV death, nonfatal heart attack or nonfatal stroke that were consistent with that observed in the overall UA/NSTEMI and STEMI populations. In the UA/NSTEMI population, the rate of the primary composite endpoint was 10 percent in patients with diabetes treated with Effient versus 15 percent in patients with diabetes treated with clopidogrel. In the STEMI population, the rate of the primary composite endpoint was 9 percent in patients with diabetes treated with Effient versus 13.6 percent in patients with diabetes treated with clopidogrel. In TRITON-TIMI 38 patients with diabetes, the risk of non-CABG TIMI major or minor bleeding was 4.9 percent for Effient versus 4.5 percent for clopidogrel. In STEMI patients, the risk of non-CABG TIMI major or minor bleeding was 4.8 percent for Effient versus 4.5 percent for clopidogrel. In the overall population TRITON-TIMI 38, the rates of non-CABG TIMI major or minor bleeding were 4.9 percent for prasugrel and 3.4 percent for clopidogrel ($p=0.002$).

In TRITON-TIMI 38, there were 50 percent fewer stent thromboses ($p<0.001$) reported among patients randomized to Effient

(0.9 percent) than among patients randomized to clopidogrel (1.8 percent). The differences manifested early and were maintained through one year of follow-up, and findings were similar with bare metal and drug-eluting stents.

Finally, Effient can be administered with drugs that are inducers or inhibitors of cytochrome P450 enzymes.

Effient is indicated to reduce the risk of future heart-related events, such as heart attack or blood clot in a stent, in patients with acute coronary syndrome (ACS) managed with a procedure called angioplasty.

About Daiichi Sankyo

The Daiichi Sankyo Group is dedicated to the creation and supply of innovative pharmaceutical products to address the diversified, unmet medical needs of patients in both mature and emerging markets. While maintaining its portfolio of marketed pharmaceuticals for hypertension, hyperlipidemia, and bacterial infections, the Group is engaged in the development of treatments for thrombotic disorders and focused on the discovery of novel oncology and cardiovascular-metabolic therapies. Furthermore, the Daiichi Sankyo Group has created a "Hybrid Business Model," which will respond to market and customer diversity and optimize growth opportunities across the value chain. For more information, please visit www.daiichisankyo.com.

Daiichi Sankyo, Inc., headquartered in Parsippany, New Jersey, is a member of the Daiichi Sankyo Group. For more information on Daiichi Sankyo, Inc., please visit www.dsi.com.

About Eli Lilly and Company

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers - through medicines and information - for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com.

Important Safety Information about Effient

Antiplatelet medicines, including Effient, can increase the risk of bleeding. If patients have unexplained or excessive bleeding while on Effient, they should contact their doctor right away as some bleeding can be serious, and sometimes may lead to death. Patients should not take Effient if they have a stomach ulcer or other conditions that cause bleeding or if they have a history of stroke or "mini-stroke" (transient ischemic attack or TIA).

If patients are 75 or older, or if they weigh less than 132 pounds, or if they are taking anticoagulants (e.g., warfarin) or taking NSAIDs (e.g., ibuprofen or naproxen) for a long time, they should talk to their doctor, as they may be at an increased risk of bleeding.

If patients plan to have surgery or a dental procedure, they should tell their doctors that they are taking Effient.

Patients should not stop taking Effient without first talking to the doctor who prescribed it for them, as this may result in increased risk of a clot in their stent, a heart attack or death.

Patients should get medical attention right away if they develop any of the following unexpected symptoms: fever, weakness, yellowing of the skin or eyes, or if skin becomes very pale or dotted with purple spots. These symptoms may be signs of a rare but potentially life-threatening condition called TTP, which has been reported with other medicines in this class.

For more information about Effient, please see the Full Prescribing Information, including Boxed Warning (<http://pi.lilly.com/us/effient.pdf>), and Medication Guide (<http://pi.lilly.com/us/effient-ppi.pdf>). You may also learn more about Effient at www.Effient.com.

This statement contains certain forward-looking statements about Effient for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndromes who are managed with percutaneous coronary intervention and reflects Daiichi Sankyo's and Lilly's current beliefs. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. There is no guarantee that future study results and patient experience will be consistent with study findings to date or that the product will be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's filing with the United States Securities and Exchange Commission and Daiichi Sankyo's filings with the Tokyo Stock Exchange. Daiichi Sankyo and Lilly undertake no duty to update forward-looking statements.

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Plavix(R) is a registered trademark of Sanofi-Aventis Corp.

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