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Refer to: Christina D. Gaines, APR
Eli Lilly and Company
317-276-3845 (office)
317-366-2568 (cell)

Kimberly Wix
Daiichi Sankyo (U.S.A.)
973-944-2338 (office)
908-656-5447 (cell)

Shigemichi Kondo
Daiichi Sankyo (Tokyo)
81-3-6225-1126 (office)

Effient® Showed Significant 26 Percent Reduction in Cardiovascular Events Over Plavix® in New Core Clinical Cohort Population Sub-Analysis of the TRITON-TIMI 38 Pivotal Study

Analysis evaluated efficacy among three patient sub-groups

PARSIPPANY, N.J. and INDIANAPOLIS (August 11, 2011) – A post-hoc analysis of an important subset of patients from the TRITON-TIMI 38 study – those identified as the "core clinical cohort" population – showed that treatment with Effient® (prasugrel) (in combination with aspirin) was associated with a 26 percent reduction in the combined primary endpoint of cardiovascular death, myocardial infarction or stroke, compared to treatment with Plavix® (clopidogrel) (8.3 vs. 11.0 percent, respectively, $p<0.0001$). This corresponds to a 2.7 percent absolute risk reduction for patients treated with Effient. The results of this analysis, which also examined clinical outcomes in two other cohorts

of patients who were treated for acute coronary syndromes (ACS) and underwent angioplasty with stenting, were recently published online in the *American Journal of Cardiology*.[1]

For this analysis, investigators analyzed three patient clinical cohorts.

- The core clinical cohort: Patients who were under 75 years of age, weighed 132 pounds or more and who had no prior history of stroke or transient ischemic attack (TIA). This group (n=10,804, 79 percent of all study subjects) excluded those patients considered to be at higher risk for bleeding by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in their regulatory approval of Effient and as outlined in prescribing labels for Effient tablets in these regions.
- The non-core cohort: Patients 75 years of age or older or patients who weighed less than 132 pounds, but without known prior stroke or TIA (n=2,149; 16 percent of study participants).
- The third group were patients with a self-reported or known history of stroke or TIA prior to enrollment (n=518; 4 percent of study participants). Effient is contraindicated in such patients.
- Patients without known prior stroke, but with missing baseline weight data were excluded from the analysis as it could not be determined to which final cohort they should be assigned to (n= 137;1 percent of study participants).

There was a tendency toward higher bleeding rates in Effient patients compared to Plavix patients. Appropriate prescribing may help minimize a bleeding risk. Based on the post hoc analysis reported in this paper, in patients in the TRITON-TIMI 38 study who were younger than 75, heavier than 132 lbs and with no prior stroke, the difference in the rates of certain types of bleeding (known as non-CABG TIMI major bleeding) was reduced, without adversely impacting the efficacy of Effient versus Plavix.

Relative bleeding rates were as follows across the core and non-core groups. In the core group, the rate of TIMI major bleeding was 1.9 percent in Effient patients compared

to 1.5 percent in Plavix patients, corresponding to a 0.4 percent absolute increase and a 24 percent relative increase in Effient patients (p= 0.17). In the non-core group, the rate of TIMI major bleeding was 4.1 percent in Effient patients compared to 3.4 percent in Plavix patients, corresponding to a 0.7 percent absolute increase and a 23 percent relative increase in Effient patients (p= 0.40). In both cases, findings were not statistically significant.

The rate of TIMI major or minor bleeding was statistically significantly greater with Effient than Plavix in the core group (3.9 percent vs. 3.0 percent respectively, p=0.033), but not in the non-core group (9.8 percent Effient vs. 7.5 percent Plavix, p=0.08), although the relative increase in bleeding within these groups were similar.

“This analysis showed that the use of prasugrel in a clinically identifiable population of ACS patients undergoing PCI in the TRITON-TIMI 38 trial significantly improved cardiovascular outcomes,” said Stephen D. Wiviott, M.D., at the TIMI Study Group, Cardiovascular Division, Brigham and Women’s Hospital and Harvard Medical School, Boston, and lead author of the paper.

The analysis found that in the ≥75 year old and low body weight (< 132 pounds) patients (the non-core cohort), event rates were high in both treatment arms (15.3 vs. 16.3 percent, p=0.61, HR=0.94) compared to the core cohort group. Patients taking Effient in the third group (described above) had non-favorable results with regard to both efficacy and safety compared to Plavix, with a higher rate of primary efficacy events (19.1 percent vs. 14.4 percent, p=0.15) driven by an increase in stroke and a higher rate of bleeding, including more intracranial hemorrhage (2.3 percent vs. 0 percent, p=0.02). Effient is contraindicated in such patients.

The TRITON-TIMI 38 trial was sponsored by Daiichi Sankyo Co., Ltd. and Eli Lilly and Company.

Study Methodology

TRITON-TIMI 38 was a head-to-head study comparing Effient (60-mg loading dose [LD], followed by a 10-mg once-daily maintenance dose) plus aspirin (ASA) with Plavix (300-mg LD, followed by a 75-mg once-daily maintenance dose) plus ASA in 13,608 patients with ACS managed with percutaneous coronary intervention (PCI), a procedure to open blockages in heart arteries, including the use of coronary stenting. The median duration of study treatment was 14.5 months.[2]

The primary endpoint of the study was the combined incidence of cardiovascular death, non-fatal heart attack or non-fatal stroke in patients followed for 6-15 months following PCI. The study showed that treatment with Effient produced a statistically significant 18 percent reduction in the relative risk of the combined measure of cardiovascular death, nonfatal heart attack or nonfatal stroke compared with Plavix in people with chest pain at rest or milder heart attacks (unstable angina/ non-ST segment myocardial infarction) (9.3 vs. 11.2 percent respectively, p=0.002) and a 21 percent significant reduction in the combined endpoint in people with more severe heart attacks (ST elevation myocardial infarction) (9.8 vs. 12.2 percent respectively, p=0.019). This corresponds to a 1.9 percent absolute risk reduction for UA/NSTEMI patients treated with Effient and a 2.4 percent absolute risk reduction for STEMI patients treated with Effient.[2] TRITON-TIMI 38 patients treated with Effient also experienced a 50 percent relative risk reduction (corresponding to 1.1 percent absolute risk reduction) in stent-related clots when compared with Plavix, regardless of stent type (1.1 percent vs. 2.2 percent respectively, p<0.001).[2] In TRITON, the risk of non-coronary artery bypass graft (non-CABG) major bleeding, including fatal bleeding, was higher with Effient (2.2 percent incidence) compared with Plavix (1.7 percent incidence) (p=0.029).[2] The rate of TIMI major or minor bleeding was significantly greater with Effient than Plavix (5.0 percent vs. 3.8 percent respectively, p=0.002). The risk of coronary artery bypass graft (CABG) major bleeding, including fatal bleeding, was higher with Effient (13.4 percent incidence) than Plavix (3.2 percent incidence) (p<0.001).[2] In TRITON-TIMI 38, the LD of Plavix was delayed relative to the placebo-controlled trials that supported its approval for ACS.

Compared with the overall study population, a higher risk of serious bleeding among Effient patients was most evident in three distinct patient populations that are readily identifiable: patients who weighed less than 132 lbs (60 kg), patients who were 75 years of age or older and patients who have had a prior transient ischemic attack (TIA) or stroke.[3] A 5 mg maintenance dose may be considered for patients who weigh less than 132 lbs.[3] Effient is generally not recommended for use in patients 75 years or older,[3] except in high risk patients (diabetes or prior MI), where its effects appears to be greater and its use may be considered.[3] Patients with prior TIA or stroke should not be treated with Effient.[3]

In this study, survival analysis methods were used to compare outcomes by treatment assignment (Effient vs. Plavix) and to compare outcomes by whether subjects were included in the core clinical cohort, non-core cohort or contraindicated cohort. The principal limitation of this analysis is that the subgroups examined were identified in a post-hoc fashion.

About Effient

Daiichi Sankyo Company, Limited (TSE: 4568), and Eli Lilly and Company (NYSE: LLY) co-developed Effient, an oral antiplatelet agent discovered by Daiichi Sankyo and its Japanese research partner, Ube Industries, Ltd. Effient helps keep blood platelets from clumping together and developing a blockage in an artery. Effient is indicated to reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients with ACS who are to be managed with an artery-opening procedure called PCI as follows: [1] patients with unstable angina (UA) or non–ST-elevation myocardial infarction (NSTEMI); [2] patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.

The loading dose of Effient is 60 mg and the maintenance dose is 10 mg once daily. Effient is available in 5-mg and 10-mg tablets. PCI usually includes the placement of a stent to help keep the artery open.

About Acute Coronary Syndrome

ACS, which includes heart attack and a type of chest pain called unstable angina, affects more than one million people in the United States annually.[4] The annual incidence of new heart attacks is estimated to be approximately 610,000 and about 325,000 people will have a recurrent attack.[4] Each year, approximately 645,000 people with ACS are managed with PCI, which typically includes the implantation of a stent that restores blood flow to blocked arteries in the heart.[5] ACS results in significant illness and death, costing Americans more than $150 billion each year.[5] Nearly 60 percent of the U.S healthcare costs of ACS are due to re-hospitalization.[5] Strategies to prevent recurrent heart attacks and re-hospitalization are important to improve patient outcomes and reduce the cost burden of ACS.[5]

Important Safety Information

What is the most important information patients should know about Effient?

Effient® (prasugrel) can cause 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 fatal. Patients should not take Effient if they currently have abnormal bleeding, such as stomach or intestinal bleeding, bleeding in their head, or have a history of stroke, or "mini-stroke" (transient ischemic attack or TIA). Patients should stop taking Effient if they have a stroke.

Whenever possible, patients should stop taking Effient at least 7 days before any surgery, as instructed by their doctor who prescribed Effient.

Patients may also have a higher risk of bleeding if they take Effient and they: a) are age 75 or older, b) weigh less than 132 pounds, c) are taking anticoagulants (eg, warfarin) or NSAIDs (eg, ibuprofen or naproxen) for a long time, d) undergo surgery, or e) have severe liver problems.

Patients should not stop taking Effient without talking to the doctor who prescribes it for them. People who are treated with angioplasty and have a stent, and stop taking Effient too soon, have a higher risk of a blood clot in the stent, having a heart attack, or dying.

What should patients tell their doctor before taking Effient?

Tell their doctor about all of their medical conditions, allergies and medicines they are taking.

What are the possible side effects of Effient?

Bleeding is the most common side effect of Effient.

TTP, a rare but potentially life-threatening condition, has been reported with Effient, sometimes after a short time (less than 2 weeks). Patients should get medical attention right away if they develop the following unexpected symptoms of TTP: fever, weakness, yellowing of the skin or eyes, or if skin becomes very pale or dotted with purple spots. Other side effects may occur.

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

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.

This press release 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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[1] Wiviott, S. *et al.* Efficacy and Safety of Intensive Antiplatelet Therapy with Prasugrel from TRITON – TIMI 38 in a Core Clinical Cohort Defined by Worldwide Regulatory Agencies. *The American Journal of Cardiology* 2011. Published online August 4, 2011. Available at: http://www.ajconline.org/article/S0002-9149(11)01906-0/abstract.

[2] Wiviott SD, Braunwald E, McCabe CH, et al; for the TRITON-TIMI 38 Investigators. N Engl J Med. 2007;357:2001-2015.

[3] Effient (prasugrel) prescribing information. Daiichi Sankyo, Inc. and Eli Lilly and Company.

[4] Roger VL, Go AS, Lloyd-Jones DM, et al. for the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2011 update. *Circulation*. 2011;123:e1-e192.

[5] Kolansky DM. Acute coronary syndromes: Morbidity, mortality, and pharmacoeconomic burden. *Amer. J. of Managed Care*. 2009;15:S36-S41.