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New Eliquis® (apixaban) Post-hoc Subanalysis of the Phase III ARISTOTLE trial Demonstrated that within 30 Days of a Procedure, Stroke or Systemic Embolism and Major Bleeding were Uncommon

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Results presented today at the ESC Congress 2013

PRINCETON, N.J. & NEW YORK--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) and Pfizer Inc. (NYSE: PFE) today announced results of a post-hoc subanalysis from the Phase III ARISTOTLE trial. Patients with nonvalvular atrial fibrillation (NVAF) who are anticoagulated to reduce the risk of stroke often undergo procedures for which temporary discontinuation of the anticoagulant prior to and following the procedure is sometimes warranted. This subanalysis describes the overall rates of key post-procedural outcomes, such as stroke or systemic embolism and major bleeding, among *Eliquis* and warfarin patients who underwent a procedure during the ARISTOTLE trial, and examined any differences in post-procedural events according to whether or not study drug was interrupted. This subanalysis was presented today at the ESC Congress 2013, organized by the European Society of Cardiology, in Amsterdam, The Netherlands.

The results showed that in the 30-day period following a procedure, rates of clinical events (stroke or systemic embolism, major bleeding, and all-cause death) were comparable in the *Eliquis* and warfarin treatment arms.

Among patients treated with *Eliquis*, event rates in the 30-day period following a procedure were similar whether *Eliquis* was stopped prior to the procedure or continued during the procedure. In patients taking warfarin, there was at least a twofold higher rate of major bleeding and death during the 30-day period following a procedure when warfarin was continued during the procedure compared to when warfarin was stopped prior to the procedure.

“For patients with NVAF who undergo procedures, the rate of anticoagulation-related adverse events appears to be similar whether the patient is chronically anticoagulated with apixaban or warfarin,” said study lead investigator Dr. Renato Lopes of Duke University Medical Center in Durham, North Carolina. “For NVAF patients for whom interruption of anticoagulation for a procedure is required, these findings suggest that using apixaban instead of warfarin, which is more challenging to stop and restart, may simplify the management of peri-operative anticoagulation in NVAF patients.”

There were 11,417 procedures in 6,162 patients from the 18,201 patients enrolled in the ARISTOTLE trial. The most common procedures were dental extraction/oral surgery, colonoscopy, upper endoscopy, and ophthalmic surgery. For 4,082 (35.8 percent) procedures, study drug was not stopped. In the 7,335 procedures (64.2 percent)

where study drug was stopped, the median time of study drug stop was four days before the procedure for both *Eliquis* and warfarin-treated patients. The procedures were classified as major if they required general anesthesia, and procedures were also classified as emergent or non-emergent by investigators.

Among patients undergoing procedures in the ARISTOTLE trial, stroke and systemic embolism were uncommon and the 30-day post-procedure rates for these events were not statistically different in the two treatment arms (0.33 percent for *Eliquis*vs. 0.53 percent for warfarin). Major bleeding occurred in a comparable number of patients 30 days post-procedure in the two treatment arms (1.57 percent for *Eliquis*vs. 1.81 percent for warfarin). In patients taking *Eliquis*, the rates of post-procedural stroke or systemic embolism and major bleeding were similar whether*Eliquis* was interrupted or continued. In patients taking warfarin, the rates of post-procedure major bleeding and death appeared higher when warfarin was continued compared to when it was interrupted.

“The current results do not include analyses for individual procedure types and therefore decisions whether to interrupt apixaban or warfarin prior to procedures should be based on consideration of procedural bleeding risk and patient thrombotic risk,” said Dr. Lopes. “In addition, further analyses, including analyses according to type of procedures and timing, are ongoing to better define these relationships.”

The U.S. Prescribing Information for *Eliquis* states that *Eliquis* should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. *Eliquis*should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled.

The U.S. Prescribing Information for *Eliquis* also includes a Boxed Warning for patients who discontinue treatment. Patients on *Eliquis* who discontinue treatment are at an increased risk of thrombotic events.

About ARISTOTLE

The ARISTOTLE study was designed to demonstrate the efficacy and safety of*Eliquis* versus warfarin for the prevention of stroke or systemic embolism. In ARISTOTLE, 18,201 patients were randomized (9,120 patients to *Eliquis* and 9,081 to warfarin). ARISTOTLE was an active-controlled, randomized, double-blind, multi-national trial in patients with nonvalvular atrial fibrillation or atrial flutter, and at least one additional risk factor for stroke. Patients were randomized to treatment with *Eliquis* 5 mg orally twice daily (or 2.5 mg twice daily in selected patients, representing 4.7 percent of all patients) or warfarin (target INR range 2.0-3.0), and followed for a median of 1.8 years.

About Atrial Fibrillation

Atrial fibrillation is the most common cardiac arrhythmia (irregular heart beat). It is estimated that approximately 5.8 million Americans and six million individuals in Europe have atrial fibrillation. The lifetime risk of developing atrial fibrillation is estimated to be approximately 25 percent for individuals 40 years of age or older. One of the most serious medical concerns for individuals with atrial fibrillation is the increased risk of stroke, which is five times higher in people with atrial fibrillation than those without atrial fibrillation. In fact, 15 percent of all strokes are attributable to atrial fibrillation in the U.S. Additionally, strokes due to atrial fibrillation are more burdensome than strokes due to other causes. Atrial fibrillation-related strokes are more severe than other strokes, with an associated 30-day mortality of 24 percent and a 50 percent likelihood of death within one year in patients who are not treated with an antithrombotic.

About *Eliquis*®

Eliquis® (apixaban) is an oral direct Factor Xa inhibitor. By inhibiting Factor Xa, a key blood clotting protein, *Eliquis* prevents thrombin generation and blood clot formation. *Eliquis* is approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation in the United States, European Union (which includes 28 member states plus Iceland and Norway), Japan and a number of other countries around the world. *Eliquis* is approved for prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery in the European Union (which includes 28 member states plus Iceland and Norway) and a number of other countries around the world. *Eliquis*is not approved for this indication in the U.S. or Japan.

IMPORTANT SAFETY INFORMATION FOR ELIQUIS

BOXED WARNING: DISCONTINUING ELIQUIS IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE.

Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered.

CONTRAINDICATIONS

- Active pathological bleeding

- Severe hypersensitivity reaction to ELIQUIS (apixaban) (i.e., anaphylactic reactions)

WARNINGS AND PRECAUTIONS

Increased Risk of Stroke with Discontinuation of ELIQUIS: Discontinuing ELIQUIS in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in patients with nonvalvular atrial fibrillation. If ELIQUIS must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant.

Bleeding Risk: ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal bleeding. Concomitant use of drugs affecting hemostasis increases the risk of bleeding including aspirin and other anti-platelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs. Patients should be made aware of signs or symptoms of blood loss and instructed to immediately report to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage. There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for about 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available. Because of high plasma protein binding, apixaban is not expected to be dialyzable. Protamine sulfate and vitamin K would not be expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated charcoal reduces absorption of apixaban thereby lowering apixaban plasma concentrations.

Prosthetic Heart Valves: The safety and efficacy of ELIQUIS has not been studied in patients with prosthetic heart valves and is not recommended in these patients.

ADVERSE REACTIONS

The most common and most serious adverse reactions reported with ELIQUIS (apixaban) were related to bleeding.

DISCONTINUATIONS FOR SURGERY AND OTHER INTERVENTIONS

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled.

DRUG INTERACTIONS

Strong Dual Inhibitors of CYP3A4 and P-gp: Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Decrease the dose of ELIQUIS to 2.5 mg twice daily when coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp, (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp.

Strong Dual Inducers of CYP3A4 and P-gp: Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke. Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort) because such drugs will decrease exposure to apixaban.

Anticoagulants and Antiplatelet Agents: Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY CATEGORY B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Please see full Prescribing Information including BOXED WARNING and Medication Guide available at www.bms.com.

About the Bristol-Myers Squibb/Pfizer Collaboration

In 2007, Pfizer and Bristol-Myers Squibb entered into a worldwide collaboration to develop and commercialize *Eliquis*, an oral anticoagulant discovered by Bristol-Myers Squibb. This global alliance combines Bristol-Myers Squibb's long-standing strengths in cardiovascular drug development and commercialization with Pfizer’s global scale and expertise in this field.

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 http://www.bms.com or follow us on Twitter at http://twitter.com/bmsnews.

Pfizer Inc.: Working together for a healthier world™

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, Pfizer has worked to make a difference for all who rely on us. To learn more, please visit us atwww.pfizer.com.

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 product development. 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. Among other risks, there can be no guarantee that Eliquis will be approved for the prevention and treatment of VTE or in the U.S. Forward-looking statements in this 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, 2012, in our Quarterly Reports on Form 10-Q and our 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.

PFIZER DISCLOSURE NOTICE:

The information contained in this release is as of August 31, 2013. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments. This release contains forward-looking information about Eliquis (apixaban), including its potential benefits, that involves substantial risks and uncertainties. Such risks and uncertainties include, among other things, (i) the uncertainties inherent in research and development; (ii) uncertainties regarding the commercial success of Eliquis; (iii) whether and when Eliquis will be approved in the EU for the treatment of venous thromboembolic events (VTE) or in the U.S. and other markets for the prevention and treatment of VTE, as well as the decisions of regulatory authorities in those jurisdictions regarding labeling and other matters that could affect the availability or commercial potential of those additional indications; and (iv) competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K/A for the fiscal year ended December 31, 2012 and in its reports on Form 10-Q and Form 8-K.

Bristol-Myers Squibb Media: Chrissy Trank, 609-252-3418 christina.trank@bms.com Investors: Ranya Dajani, 609-252-5330 ranya.dajani@bms.com Ryan Asay, 609-252-5020 ryan.asay@bms.com or Pfizer Inc. Media: Jennifer Kokell, 212-733-2596 jennifer.kokell@pfizer.com Investors: Suzanne Harnett, 212-733-8009 suzanne.harnett@pfizer.com