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# Bristol-Myers Squibb and Pfizer Present Investigational Eliquis® (apixaban) Data for Patients with Non-Valvular Atrial Fibrillation (NVAF) Undergoing Cardioversion

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Data presented at ESC Congress 2017; highlighted in official hot line presentation and press program

Bristol-Myers Squibb Company (NYSE:BMY) and Pfizer Inc. (NYSE:PFE) today presented findings from EMANATE (Eliquis evaluated in acute cardioversion coMpared to usuAl treatmeNts for AnTicoagulation in subjEcts with NVAF), a Phase 4 clinical trial, during a late-breaking hot line presentation at the ESC Congress 2017, organized by the European Society of Cardiology, in Barcelona, Spain. This descriptive, randomized, open-label trial explored the safety and efficacy of apixaban 5 mg twice daily (2.5 mg lower dose when two of the following were present: age ?80 years, weight ?60 kg, or serum creatinine ?1.5 mg/dL (133?mol/L)) vs. standard of care (parenteral heparin and/or vitamin K antagonist). The outcomes measured in this study were the occurrence of acute stroke, systemic embolism, major bleeding, clinically relevant non-major bleeding and all-cause death in non-valvular atrial fibrillation patients undergoing cardioversion. This is an investigational use for Eliquis. Eliquis is not FDA-approved for the reduction of stroke in NVAF patients undergoing cardioversion (please see indications and important safety information for Eliquis later in the press release).

Cardioversion, which could be achieved pharmacologically, through electrical shock, or through both means, could quickly restore a heart's normal rhythm.1 A concern related to cardioversion is the potential for a blood clot in the heart to travel to the brain (stroke) or other areas (systemic embolism). Guidelines recommend that patients being considered for cardioversion require at least three weeks of oral anticoagulation to minimize the potential of cardioversion-related stroke.2,3 However, delaying patient intervention could make it increasingly difficult to achieve and maintain normal heart rhythm.iii Patients with NVAF may undergo early cardioversion at the discretion of a cardiologist or emergency room physician to enable the heart to pump more effectively.

"The EMANATE trial exemplifies the Bristol-Myers Squibb-Pfizer Alliance's commitment to expanding understanding of the utility of Eliquis across broad NVAF patient populations and clinical settings," said Rory O'Connor, M.D., Chief Medical Officer, Pfizer Innovative Health. "These exploratory findings add to the growing body of knowledge for Eliquis in different NVAF patients, including those at higher-risk."

This EMANATE study randomized patients with recently diagnosed NVAF who were anticoagulation-naïve (defined as having received less than 48 hours of anticoagulation) to either apixaban or standard of care (warfarin with or without heparin). The study protocol encouraged the use of image guidance according to the guidelines to determine the absence of a clot in the heart, allowing earlier cardioversion, or anticoagulation for a minimum of three weeks before cardioversion. Anticoagulation was administered from randomization until 30 days after cardioversion. If cardioversion was not performed, anticoagulation was to be administered for a maximum of 90 days. The apixaban dose was 5 mg twice daily (or dose reduced per standard criteria). If the

imaging study showed no clot in the heart, five doses of apixaban were administered to achieve steady-state blood levels before cardioversion. Alternatively, if no clot was detected, an immediate cardioversion could be undertaken following a single 10 mg loading dose of apixaban (or dose reduced per standard criteria) administered at least two hours before cardioversion, followed by a maintenance regimen. The loading dose enabled patients to quickly attain steady state-like concentrations of anticoagulation, allowing for earlier cardioversion.

Results showed that, in the intent-to-treat (ITT) population (n=1500; Eliquis n=753, heparin/VKA n=747), there were no strokes or systemic emboli in the Eliquis group compared to six strokes (one hemorrhagic and five ischemic) and no systemic emboli in the standard of care group. In the safety analysis population (n=1436; Eliquis n=735, heparin/VKA n=721), which included all patients receiving one dose of study drug, there were numerically fewer major bleeding events in the apixaban treatment group (n=3) than those randomly assigned to standard of care (n=6), and numerically fewer clinically relevant non-major bleeding events in the apixaban treatment group (n=11) than those randomly assigned to standard of care (n=13). It is important to note that Eliquis increases the risk of bleeding and can cause serious, potentially fatal, bleeding. There were two deaths in the Eliquis group (one due to acute alcoholic hepatitis prior to dosing, and one due to complications related to perforation of the colon) and one in the standard of care group.

“The current standard of care for reducing the risk of stroke in the setting of cardioversion is heparin and warfarin, which require monitoring and potential dose adjustment. This can delay performing cardioversion,” said Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Professor of Medicine in the Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia and Lankenau Medical Center and Bryn Mawr Hospital. “The EMANATE study points to apixaban as a potential alternative approach. Further research is merited to confirm these findings.”

“Clinicians often prefer cardioversion earlier after a patient is diagnosed with non-valvular atrial fibrillation because the sooner the intervention, the more likely the patient is able to revert back to a regular heart rhythm,” said Christoph Koenen, M.D., MBA, VP, Development Lead, Eliquis, Bristol-Myers Squibb. “These exploratory data offer preliminary insights into the potential effects of Eliquis in this high-risk clinical setting. Further investigation is needed to better understand anticoagulation for early cardioversion.”

**About Eliquis**

Eliquis (apixaban) is an oral selective Factor Xa inhibitor. By inhibiting Factor Xa, a key blood clotting protein, Eliquis decreases thrombin generation and blood clot formation. Eliquis is approved for multiple indications in the U.S. based on efficacy and safety data from multiple Phase 3 clinical trials. Eliquis is a prescription medicine indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF); for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery; for the treatment of DVT and PE; and to reduce the risk of recurrent DVT and PE, following initial therapy.

**ELIQUIS Important Safety Information**

**WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA**

**(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.**

**(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:**

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

**Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.**

**Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.**

**CONTRAINDICATIONS**

- **Active pathological bleeding**
- **Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)**

**WARNINGS AND PRECAUTIONS**

- **Increased Risk of Thrombotic Events after Premature Discontinuation: Premature discontinuation of any oral anticoagulant, including 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 atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, 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 antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.**
- **Advise patients of signs and symptoms of blood loss and to report them immediately or go 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 at least 24 hours after the last dose (i.e., about two half-lives). A specific antidote for ELIQUIS is not available.**
- **Spinal/Epidural Anesthesia or Puncture: Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.**

**The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of**

**ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.**

**Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.**

- **Prosthetic Heart Valves: The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.**
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy: Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.**

**ADVERSE REACTIONS**

- **The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.**

**TEMPORARY INTERRUPTION 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. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.**

**DRUG INTERACTIONS**

- **Strong Dual Inhibitors of CYP3A4 and P-gp: Inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp.**
- **Strong Dual Inducers of CYP3A4 and P-gp: 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 and increase the risk of stroke and other thromboembolic events.**
- **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 U.S. Prescribing Information, including BOXED WARNINGS and Medication Guide, available at www.bms.com.**

**Local prescribing information may vary between countries. Please refer to your local Prescribing Information, including details on indications, dosage, and safety.**

**About the Bristol-Myers Squibb/Pfizer Collaboration**

**In 2007, Pfizer and Bristol-Myers Squibb entered into a worldwide collaboration to develop and commercialize apixaban, 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 about Bristol-Myers Squibb, visit us at BMS.com or follow us on LinkedIn, Twitter, YouTube and Facebook.**

**About 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, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.pfizer.com. In addition, to learn more, please visit us on www.pfizer.com and follow us on Twitter at @Pfizer and @Pfizer_News, LinkedIn, YouTube and like us on Facebook at Facebook.com/Pfizer.**

**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. 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, 2016, 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 28, 2017. 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 that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including, without limitation, the ability to meet anticipated clinical trial commencement and completion dates as well as the possibility of unfavorable clinical trial results, including unfavorable new clinical data and additional analyses of existing clinical data; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of Eliquis; and competitive developments.**

**A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2016 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the SEC and available at www.sec.gov and www.pfizer.com.**

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**1 MayoClinic.org. Accessed: July 24, 2017. http://www.mayoclinic.org/home/ovc-20336882.**
**2 January, C. T., et. al (2014). 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation. Journal of the American College of Cardiology , 64(21), 1-76. Retrieved August 08, 2017.**
**3 Kirchhof, P., et. al (2016). 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Society of Cardiology, 1-90. Retrieved August 08, 2017. 10.1093/europace/euw295**

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