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Bristol-Myers Squibb and Pfizer Enroll First Patient in Phase 4 AUGUSTUS Trial to Evaluate Safety of Eliquis (apixaban) in Nonvalvular Atrial Fibrillation Patients with a Recent Acute Coronary Syndrome or Undergoing Percutaneous Coronary Intervention

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With the first patient now enrolled in AUGUSTUS, we will be collecting data that will help inform the safety profile of Eliquis for NVAF patients who have suffered a recent ACS and/or are undergoing PCI.

Bristol-Myers Squibb Company and Pfizer Inc. today announced that the first patient has been enrolled into the Phase 4 clinical trial, AUGUSTUS. This two-by-two factorial, randomized controlled trial will evaluate the safety of *Eliquis* versus warfarin or other vitamin K antagonists (VKA) in patients with nonvalvular atrial fibrillation (NVAF) and a recent acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI), also known as a stent. In addition, patients will also be randomized to aspirin or placebo. All patients will receive a P2Y12 inhibitor (such as clopidogrel) in combination with either *Eliquis* or a VKA. *Eliquis* is approved to reduce the risk of stroke and systemic embolism in patients with NVAF.

“Limited data are available to inform the use of *Eliquis* and other oral anticoagulants in NVAF patients who require concomitant dual antiplatelet therapy,” said Renato D. Lopes, M.D., MHS, Ph.D., Duke Clinical Research Institute (DCRI) director of clinical events classification and principle investigator for AUGUSTUS. “With the first patient now enrolled in AUGUSTUS, we will be collecting data that will help inform the safety profile of *Eliquis* for NVAF patients who have suffered a recent ACS and/or are undergoing PCI.”

“This trial is critical as patients with NVAF frequently have concomitant coronary artery disease, which may result in an ACS event or require PCI that requires antiplatelet therapy.” said John H. Alexander, M.D., MHS, FACC, director of cardiovascular research at the DCRI and chair of the AUGUSTUS executive committee.

AUGUSTUS is anticipated to enroll 4,600 eligible patients from 30 countries. The two-by-two factorial design permits for the testing of two hypotheses in the study population. First, it will evaluate whether or not *Eliquis* is noninferior to a VKA on the combined outcome of major bleeding and clinically relevant non-major (CRNM) bleeding when studied in an open-label manner. Second, in a double-blind manner, it will evaluate whether or not the addition of aspirin to an anticoagulant and P2Y12 inhibitor results in significantly more major and CRNM bleeding in the study population.

Secondary objectives include the comparison of *Eliquis* to VKA (with concomitant P2Y12 therapy) for superiority on major or CRNM bleeding; death, stroke, myocardial infarction, stent thrombosis, urgent revascularization, or re-hospitalization for any cause; and the comparison of a P2Y12 inhibitor plus aspirin versus a P2Y12 inhibitor alone with either *Eliquis* or VKA with respect to death, stroke, myocardial infarction, stent thrombosis, or urgent revascularization and re-hospitalization for any cause.

The study population will include men and women age 18 and older with NVAF with the planned or existing use of an oral anticoagulant for reducing the risk of thromboembolism. In addition, participants must have had an ACS or PCI with a stent within the prior 14 days, as well as planned use of an approved P2Y12 inhibitor for at least six months.

AUGUSTUS is one of several new clinical trials that will help provide additional information on the safe and appropriate use of*Eliquis* for certain specific types of patients within currently approved indications.

About Atrial Fibrillation

Atrial fibrillation (AF) is the most common type of heartbeat disorder, or irregular heartbeat. Nonvalvular atrial fibrillation (NVAF) refers to cases in which the AF occurs in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair. It was estimated that in 2014, 6.4 million people in the U.S. and in 2010, over six million individuals in Europe, had AF. The lifetime risk of AF 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 AF is the increased risk of stroke, which is five times higher in people with AF than those without AF. Additionally, AF-related strokes tend to be more severe than other strokes with an associated 30-day mortality rate of 24 percent and a 50 percent likelihood of death within one year.

About Acute Coronary Syndrome

Acute coronary syndrome (ACS) is a term used to describe situations in which the blood supplied to the heart muscle is suddenly blocked, and includes myocardial infarction (MI), also known as a heart attack, and unstable angina (sudden, severe chest pain that typically occurs when a person is at rest). ACS affects an estimated 1.4 million people in the U.S. and an estimated 1.38 million people in Europe. ACS is a subcategory of coronary artery disease (CAD), the most common type of cardiovascular disease. Cardiovascular diseases are the number-one cause of death worldwide. According to the World Health Organization, CAD alone resulted in 7.4 million deaths during 2012.

About Percutaneous Coronary Intervention

Percutaneous coronary intervention (PCI), also known as coronary angioplasty, is a procedure used to open blocked or narrowed coronary arteries. Angioplasty also is used as an emergency procedure during a heart attack. According to the Centers for Disease Control and Prevention, there are approximately 500,000 PCIs performed annually in the U.S. alone.

About *Eliquis*

Eliquis 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 seven Phase 3 clinical trials. *Eliquis* is a prescription medicine indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular 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 Indications and Important Safety Information

Indications

ELIQUIS is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

ELIQUIS is indicated 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.

ELIQUIS is indicated 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.

PREGNACNY 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 WARNINGS 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 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, please visit www.bms.com or follow us on Twitter at http://twitter.com/bmsnews.

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, Pfizer has worked to make a difference for all who rely on us. To learn more, please visit us at www.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. 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, 2014, 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 September 9, 2015. 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, 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, 2014 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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