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Secondary Analysis of AMPLIFY-EXT Examining Predictors of Hospitalization Presented at ESC Congress: Eliquis (apixaban) Significantly Reduced the Risk of All-Cause Hospitalization Versus Placebo in Patients with Venous Thromboembolism (VTE)

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Bristol-Myers Squibb Company (NYSE:BMY) and Pfizer Inc. (NYSE:PFE) today announced results of a pre-specified secondary analysis of the *Eliquis* Phase 3 AMPLIFY-EXT trial **(A**pixaban after the initial **M**anagement of**P**u**L**monary embol**I**sm and deep vein thrombosis with **F**irst-line therap**Y**-**EXT**ended Treatment). The analysis evaluated clinical and demographic predictors of all-cause hospitalization in patients with VTE, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Results from this analysis demonstrated that during the 12-month extended treatment of VTE, *Eliquis* significantly reduced the risk of hospitalization versus placebo. This effect was independent of other variables including renal function, the only other significant predictor of hospitalization in the AMPLIFY-EXT population. These data were presented during an oral session today in Barcelona, Spain, at the ESC Congress 2014.

“The results of this AMPLIFY-EXT secondary analysis showed that *Eliquis* significantly reduced the risk of hospitalization, irrespective of other variables,” said Dr. Alexander T. Cohen, study investigator and consultant physician, Department of Hematology, Guy’s and St. Thomas’ Hospitals, King’s College, London. “The findings from this secondary analysis provide additional support for extended anticoagulation with *Eliquis* in VTE patients.”

AMPLIFY-EXT was a randomized, double-blind, placebo-controlled extended treatment superiority study with 12 months of treatment plus one month follow-up in patients with VTE who completed six to 12 months of anticoagulation therapy. The secondary analysis presented today showed that, compared with placebo, *Eliquis* 2.5 mg (p=0.032) and 5 mg (p=0.004) were both associated with significant reduction in all-cause hospitalization. Of the 2,486 patients included in the AMPLIFY-EXT trial, 138 patients were hospitalized at least once, including 62 (7.48%) in the placebo group (n=829), 42 (5.00%) in the *Eliquis* 2.5 mg group (n=840), and 34 (4.18%) in the *Eliquis* 5 mg group (n=813). Of the first hospitalizations in the placebo group, a total of 32 (51.6%) were attributed to VTE recurrence versus six (17.7%) in the*Eliquis* 5 mg group and 11 (26.2%) in the *Eliquis* 2.5 mg group.

The following factors were clinically significant and independent predictors of all-cause hospitalization during the trial:

- *Eliquis* 2.5 mg versus placebo (HR=0.65, 95% CI=0.43-0.96)
- *Eliquis* 5 mg versus placebo (HR=0.54, 95% CI=0.36-0.83)
- Severe or moderate renal impairment versus normal renal function (HR=2.26, 95% CI=1.30-3.92).

Sex, age, baseline body weight and type of VTE did not significantly predict hospitalization.

A total of 14 Bristol-Myers Squibb/Pfizer alliance-sponsored abstracts, including the AMPLIFY-EXT pre-specified secondary analysis described above, were accepted for presentation at the ESC Congress 2014.

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 to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation in the United States, European Union, Japan and a number of other countries around the world. *Eliquis* is approved for prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery in the United States, European Union and a number of other countries around the world. *Eliquis* is not approved for this indication in Japan. *Eliquis* is approved for the treatment of DVT and PE, and prevention of recurrent DVT and PE following initial therapy in the United States and European Union.

ELIQUIS 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.

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 anti-platelet 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 CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses greater than 2.5 mg twice daily, the dose of ELIQUIS should be decreased by 50% when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin). For patients receiving 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:** 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 Prescribing Information, including BOXED WARNINGS and Medication Guide, available at www.bms.com.

About DVT and PE

VTE encompasses two serious conditions: DVT, a blood clot in a deep vein, usually in the lower leg, thigh, or pelvis, which partially or totally blocks the flow of blood; and PE, a blood clot that blocks one or more vessels in the lungs. Approximately one million patients in the EU are diagnosed every year with VTE. In the U.S., the number of adults with VTE is projected to more than double from 950,000 in 2006 to 1.82 million in 2050. Once a VTE has occurred, approximately 33% of patients may experience a recurrence within 10 years.

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 http://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.

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