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Bristol-Myers Squibb and Pfizer Alliance Announce Real-World Observational Analysis of the Effectiveness and Safety of Direct Oral Anticoagulants Compared to Warfarin in Elderly Patients with Non-Valvular Atrial Fibrillation

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Eliquis® (apixaban) associated with lower risk of stroke and lower rates of major bleeding compared to warfarin in U.S. Humana database analysis

Bristol-Myers Squibb Company (NYSE: BMY) and Pfizer Inc. (NYSE: PFE) today announced findings from a real-world data analysis of the U.S. Humana database, in which treatment with Eliquis® (apixaban) was associated with a significantly lower risk of stroke/systemic embolism and lower rates of major bleeding compared to warfarin in patients aged 65 years and older with non-valvular atrial fibrillation (NVAF). The Humana database includes managed care medical and pharmacy claims from greater than 20 million persons primarily residing in the Southern and Midwestern regions of the U.S. This analysis was published today in the journal Current Medical Research and Opinion, with data from select cohorts also presented today in a poster session at the ESC Congress 2017, organized by the European Society of Cardiology, in Barcelona, Spain (please see indications and important safety information for Eliquis later in this press release).

In this observational, real-world data analysis, NVAF patients with U.S. Medicare Advantage insurance were identified in the Humana database by age (65 years and older), and having a pharmacy claim of Eliquis or warfarin between January 1, 2013, and September 30, 2015. The analysis evaluated rates of stroke/systemic embolism (including ischemic stroke, hemorrhagic stroke and systemic embolism) and major bleeding (including intracranial hemorrhage, gastrointestinal bleeding, and other major bleeding). Rates of stroke/systemic embolism and major bleeding were evaluated in the follow-up, based on hospitalization claims with the corresponding ICD-9-CM codes at the first position among the diagnosis codes associated with any of the inpatient claims. Real-world data analyses cannot be used as stand-alone evidence to validate the efficacy and/or safety of a treatment. Observational real-world studies can only evaluate association and not causality.i,ii Please see full methodology and additional limitations below.

“NVAF has long been identified as a significant risk for stroke, and its prevalence increases with age,” said Steven Deitelzweig, M.D., lead author of the publication and System Department Chair of Hospital Medicine, Ochsner Medical Center, New Orleans. “Real-world data such as this Humana database analysis provide further information to inform treatment decisions for select patient sub-populations, such as the elderly, in our everyday clinical practice.”

Eliquis, in this analysis, was associated with a lower risk of stroke/systemic embolism (hazard ratio [HR]:0.65, 95% confidence interval [CI]: 0.51 to 0.83, p=0.001) and lower rates of major bleeding (HR:0.53, 95% CI: 0.45 to 0.63, p=0.001) compared to warfarin. The mean duration of follow-up was 6.3 months for Eliquis and 8.3 months for warfarin. These findings supplement results from the landmark Phase 3 ARISTOTLE (Apixaban for Reduction In STroke and Other ThromboembоLic Events in Atrial Fibrillation) clinical trial. Eliquis increases the risk of bleeding and can cause serious, potentially fatal, bleeding.

This analysis is part of the BMS-Pfizer Alliance global real-world data analysis program, ACROPOLIS™ (Apixaban ExperienCe Through Real-WOrld POpuLatIon Studies). Data sources for ACROPOLIS include de-identified medical records, medical and pharmacy health insurance claims data, and national health data systems, representing patient records across various populations and geographies.

“People aged 65 and older with non-valvular atrial fibrillation are approximately three to five times more likely to have a stroke than those without this disorder,”iii,iv,v said Christoph Koenen, M.D., MBA, VP, Development Lead, Eliquis, Bristol-Myers Squibb (BMS). “Despite treatment advances over the past decade, a significant number of people in this age group with NVAF remain under-treated.”vi

“Through these real-world analyses, we continue to add to the growing body of evidence around the effects of Eliquis in commonly seen patient groups such as the elderly,” said Rory O’Connor, M.D., Chief Medical Officer, Pfizer Innovative Health. “The analyses from the ACROPOLIS program aim to supplement Eliquis’ randomized clinical trial results with insights gleaned from data collected across large patient populations and diverse clinical settings.”

Methodology

In addition to the Eliquis cohort, this observational, retrospective analysis of the Humana database included two other direct oral anticoagulants (rivaroxaban and dabigatran). The analysis was conducted in patients aged 65 and older with NVAF who had not received an oral anticoagulant for at least one year. Patients had to have continuous health plan enrollment with medical and pharmacy benefits for at least 12 months pre-index date. Patients with claims indicative of diagnoses of valvular heart disease, venous thromboembolism, transient atrial fibrillation, cardiac surgery, hyperthyroidism and thyrotoxicity, or pregnancy during the baseline period were excluded. For more information, please refer to the full journal article published in Current Medical Research and Opinion.

In this analysis, 7,107 matched pair patients were identified as treated with Eliquis and warfarin respectively (n=14,214) after balancing patient characteristics with propensity score matching (PSM). Multivariate logistic regression was used in this analysis to generate propensity scores with covariates to balance select demographic and clinical characteristics. Separate one-to-one PSM was conducted among patients treated with Eliquis vs. warfarin to verify cohorts were well balanced with key patient characteristics not statistically different (p>0.05). Cox proportional hazards models were used to estimate the hazard ratio (HR) – the rates at which events occurred – of stroke/systemic embolism and major bleeding using primary ICD-9 codes of inpatient claims.

Limitations of Real-World Data Analyses and of the Humana Database Analysis

Real-world data have the potential to supplement randomized clinical trial data by providing additional information about how a medicine performs in routine medical practice. Real-world data analyses have several limitations. For example, the source and type of data used may limit the generalizability of the results and of the endpoints. Observational real-world studies can only evaluate association and not causality. Due to these limitations, real-world data analyses cannot be used as stand-alone evidence to validate the efficacy and/or safety of a treatment. It is important to note that, at this time, there are no head-to-head clinical trials comparing direct

oral anticoagulants.

In this analysis, although PSM was used to control for multiple confounders, there is still potential for residual bias. Claims for a filled prescription do not indicate that the medication was consumed or taken as prescribed. Also, medications filled over-the-counter or provided as samples are not captured in the claims data. Lastly, the Humana insurance claims database is comprised of claims of persons primarily residing in the Southern and Midwestern regions of the U.S. and the results of this study may not be generalizable to the entire U.S. elderly population.

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 ACROPOLIS™

ACROPOLIS™ (Apixaban ExperienCe Through Real-WOrld POpuLatIon Studies) is the Eliquis (apixaban) global real-world data program designed to generate additional evidence from routine clinical practice settings to further inform healthcare decision makers, including healthcare providers and payers. The ACROPOLIS program will include retrospective, outcomes-based analyses from over 10 databases around the world, including medical records, medical and pharmacy health insurance claims data, and national health data systems.

Analyses of real-world data allow for a broader understanding of patient outcomes associated with Eliquis outside of the clinical trial setting, as well as insight into other measures of healthcare delivery, such as hospitalization and costs.

About ARISTOTLE

ARISTOTLE (Apixaban for Reduction In STroke and Other ThromboembоLic Events in Atrial Fibrillation) was designed to evaluate 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 non-valvular 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 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 29, 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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