



Findings Released from Real-World Data Analysis of Eliquis (apixaban) for the Treatment of Venous Thromboembolism in Patients with Active Cancer

Saturday, December 07, 2019 - 04:00pm

Results highlighted in two oral presentations at the American Society of Hematology Annual Meeting

PRINCETON, N.J. & NEW YORK--(BUSINESS WIRE)--The Bristol-Myers Squibb-Pfizer Alliance today announced results from retrospective real-world data analyses reporting outcomes on the safety and effectiveness of Eliquis® (apixaban) compared to low molecular weight heparin (LMWH) or warfarin for the treatment of venous thromboembolism (VTE) in patients with active cancer (n=14,086). The real-world data analyses were highlighted during oral presentations at the American Society of Hematology (ASH) Annual Meeting in Orlando, Florida. Results from the primary analysis showed that Eliquis use was associated with lower rates of major bleeding (MB) (hazard ratio [HR]: 0.63, 95% confidence interval [CI]: 0.47-0.86, p=0.003), clinically-relevant non-major (CRNM) bleeding (HR: 0.81, 95% CI: 0.70-0.94, p=0.006) and recurrent VTE (HR: 0.61, 95% CI: 0.47-0.81, p=0.001) compared to LMWH. Eliquis was also associated with a lower rate of recurrent VTE (HR: 0.68, 95% CI: 0.52-0.90, p=0.007) and similar rates of major bleeding (HR: 0.73, 95% CI: 0.53-1.0, p=0.051) and CRNM bleeding (HR: 0.89, 95% CI: 0.77-1.04, p=0.145) compared to warfarin. Outcomes were defined based on diagnosis codes and setting of care.

In a second oral presentation, results from a sub-group analysis of the primary study were highlighted based on different levels of risk for developing recurrent VTE, a blood clot most often found in the legs or lungs. Study findings were generally consistent with the primary analysis. It is important to note that, anticoagulants, including Eliquis, increase the risk of bleeding and can cause serious, potentially fatal bleeding. Please see important safety information below for Eliquis, including BOXED WARNINGS.

“Real-world evidence analyses such as this have the potential to provide additional insights into complex patient populations such as those with VTE and active cancer,” said Alexander Cohen, M.D., Consultant Physician, Department of Hematology at Guy’s and St. Thomas’ NHS Foundation Trust. “Results from these analyses are a welcomed addition to the growing body of data around recurrent VTE in patients with active cancer.”

VTE is the third most common cause of vascular death after heart attack and stroke.ⁱ VTE can be a major health problem among patients with cancer, with studies showing that patients with cancer are at a significantly increased risk for VTE compared to those without cancer.ⁱⁱ VTE is also a leading cause of death in cancer patients, and a significant predictor for all-cause mortality.^{iii,iv}

In these real-world analyses, four U.S. commercial insurance claims databases were used to identify VTE patients with active cancer (defined as cancer diagnosis or cancer treatment [chemotherapy, radiation and/or cancer-related surgery] within six months before or 30 days after VTE diagnosis) who initiated apixaban, LMWH, or warfarin within 30 days following the first VTE event. The risk of events was evaluated using a Cox proportional hazard model. Inverse probability treatment weighting (IPTW) was used to balance patient characteristics between apixaban, LMWH, and warfarin cohorts. Patients were followed to the earliest of: health plan disenrollment, death, index therapy discontinuation, switch to another anticoagulant, study end, or a maximum of 6 months. This was done to evaluate the rates of MB, CRNMB, and recurrent VTE (fatal or non-fatal) among VTE patients with active cancer prescribed apixaban, LMWH, or warfarin in routine clinical practice.

“Cancer and VTE are closely linked. Patients with cancer have shown to be at increased risk of developing a blood clot,” said Roland Chen, M.D., Vice President, Head of Clinical Development, Innovative Medicines, Bristol-Myers Squibb. “Given this risk and the medical complexities in patients with active cancers, it is important to increase awareness of symptoms related to VTE and bolster the visibility of this patient population to help improve health outcomes.”

Real-world data have the potential to complement randomized, controlled clinical trial data by providing additional information about how a medicine performs in routine medical practice. Real-world data analyses also have several limitations. For example, the source and type of data used may limit the generalizability of the results and endpoints. Observational real-world studies can only evaluate association and not causality, and despite the use of methods to address measured confounding, residual confounding may still be present. Due to these limitations, real-world data analyses are not used as stand-alone evidence to validate the efficacy and/or safety of a treatment. Additionally, data regarding cancer stage, laboratory test results, biomarkers, and medications prescribed during hospitalization were not available. Mortality and fatal recurrent VTE could not be evaluated because commercial databases do not have complete death information.

“There is a growing opportunity to use real-world evidence to help inform the medical community, especially within complex patient populations, including those with active cancer and VTE,” said Rory O’Connor, M.D., Chief Medical Officer, Pfizer Internal Medicine. “Data from real-world settings helps provide a more robust understanding of these patients and adds to the extensive body of real-world evidence evaluating the safety and effectiveness of Eliquis.”

BMS-Pfizer Alliance Real-World Data Program: These analyses are part of the Bristol-Myers Squibb-Pfizer Alliance global real-world data analysis program, ACROPOLIS™ (Apixaban ExperienCe Through Real-WOrld POpuLatIon Studies), designed to generate additional evidence from routine clinical practice settings to further inform healthcare decision makers, including healthcare providers and payers. These analyses 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. The ACROPOLIS program currently includes analyses of patients from more than 20 databases around the world, including anonymized medical records, medical and pharmacy health insurance claims data, and national health data systems. To date, the ACROPOLIS program includes a sample size of more than two million lives spanning more than 10 countries.

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. The approval of Eliquis for stroke risk reduction in patients with NVAf is based on data from the Phase 3 ARISTOTLE and AVERROES studies

of Eliquis in patients with NVAF. The approval of Eliquis for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the reduction in the risk of recurrent DVT and PE following initial therapy, is based on data from the global AMPLIFY and AMPLIFY-EXT studies.

U.S. FDA-Approved Indications for Eliquis: Eliquis is a prescription medicine indicated in the U.S. to reduce the risk of stroke and systemic embolism in patients with 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. The anticoagulant effect apixaban can be expected persist for at least 24 hours after the last dose (i.e., about two half-lives). An agent to reverse the anti-factor Xa activity of apixaban is available. Please visit www.andexxa.com for more information on availability of a reversal agent. **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. Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome (APS): Direct-acting oral anticoagulants (DOACs), including ELIQUIS, are not recommended for use in patients with triple-positive APS. For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

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

Combined P-gp and Strong CYP3A4 Inhibitors: Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) 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 combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or ritonavir). In

patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with combined P-gp and strong CYP3A4 inhibitors. Clarithromycin Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS. Combined P-gp and Strong CYP3A4 Inducers: Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (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

The limited available data on ELIQUIS use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery, and in the fetus and neonate. Labor or delivery: ELIQUIS use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider use of a shorter acting anticoagulant as delivery approaches.

LACTATION

Breastfeeding is not recommended during treatment with ELIQUIS.

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 about Bristol-Myers Squibb, visit us at BMS.com or follow us on

LinkedIn , Twitter , YouTube, Facebook and Instagram.

About Pfizer Inc.: Breakthroughs that change patients' lives

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, including innovative medicines and vaccines. 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](https://www.facebook.com/Pfizer).

Bristol-Myers Squibb Forward-Looking Statement

This press release contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 regarding, among other things the research, development and commercialization of pharmaceutical products. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements are based on historical performance and current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. These risks, assumptions, uncertainties and other factors include, among others, that future study results will be consistent with the results to date, that Eliquis may not achieve its primary study endpoints or receive regulatory approval for the additional indication described in this release in the currently anticipated timeline or at all and, if approved, whether such product candidate for such additional indication described in this release will be commercially successful. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect Bristol-Myers Squibb's business and market, particularly those identified in the cautionary statement

and risk factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2018, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, Bristol-Myers Squibb undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

Pfizer Disclosure Notice

The information contained in this release is as of December 7, 2019. 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 endpoints, commencement and/or completion dates for our clinical trials, as well as the possibility of unfavorable clinical trial results, including the possibility of unfavorable new clinical data and further analyses of existing clinical data; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or 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, 2018 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 U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

Eliquis® and the Eliquis logo are trademarks of Bristol-Myers Squibb Company.

i Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet* 2012;379:1835-1846 ii Timp JF, Braekkan SK, Versteeg HH, et al. Epidemiology of cancer-associated venous thrombosis. *Blood* 2013; 122: 1712-23 iii Khorana AA. Venous Thromboembolism and Prognosis in Cancer. *Thromb Res* 2010;

125(6): 490-493 in Centers for Disease Control and Prevention (CDC). Deep Vein Thrombosis & Pulmonary Embolism.

<https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-by-air-land-sea/deep-vein-thrombosis-and-pulmonary-embolism>. Accessed November 5, 2019.

Bristol-Myers Squibb Media: media@bms.com 609-252-3345 Susan Francis, 609-529-0676, susan.francis@bms.com Investors: Timothy Power, 609-252-7509, timothy.power@bms.com Pfizer Inc. U.S. Media: Steven Danehy 212-733-1538, steven.danehy@pfizer.com Investors: Ryan Crowe, 212-733-8160, ryan.crowe@pfizer.com