Pfizer Logo

European Commission Approves Eliquis (apixaban) for the Treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), and Prevention of Recurrent DVT and PE

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In the AMPLIFY trial, Eliquis was shown to be non-inferior for the treatment of recurrent venous thromboembolism (VTE)/VTE-related death and was statistically superior in the primary safety endpoint of major bleeding vs. enoxaparin/warfarin In the AMPLIFY-EXT trial, Eliquis demonstrated a superior reduction in VTE/all-cause death with no statistical difference in major bleeding events vs. placebo

Bristol-Myers Squibb Company (NYSE:BMY) and Pfizer Inc. (NYSE:PFE) today announced that the European Commission has approved *Eliquis* for the treatment of DVT and PE, and the prevention of recurrent DVT and PE in adults. The European Commission approval applies to all European Union (EU) member states as well as Iceland and Norway. *Eliquis* is also approved in the EU for the prevention of venous thromboembolism (VTE) in adults who have undergone elective total hip or knee replacement surgery, and for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors.

“Every year, approximately one million patients in the EU are diagnosed with VTE,” said Dr. Elliott Levy, senior vice president, head of Specialty Development, Bristol-Myers Squibb. “Once a VTE has occurred, approximately 33 percent of patients may experience a recurrence within 10 years.”

The marketing authorization for *Eliquis* follows the positive opinion issued by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency, and is supported by two pivotal Phase 3 clinical trials, AMPLIFY and AMPLIFY-EXT. AMPLIFY (**A**pixaban for the initial **M**anagement of **P**u**L**monary embol**I**sm and deep vein thrombosis as **F**irst-line therap**Y**) was designed to demonstrate the efficacy and safety of *Eliquis* for the treatment of DVT and PE versus enoxaparin 1 mg/kg twice daily subcutaneously for at least 5 days (until INR? 2) and warfarin (target INR range 2.0-3.0) orally for six months. AMPLIFY-EXT (**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) was designed to demonstrate the efficacy and safety of *Eliquis* compared to placebo for the prevention of recurrent DVT and PE following six to 12 months of anticoagulant treatment for DVT and/or PE.

“The European Commission’s approval of *Eliquis* for the treatment of DVT and PE and the prevention of recurrence is an important milestone and demonstrates Bristol-Myers Squibb and Pfizer’s ongoing commitment to bringing innovative medicines to patients who need them,” said Steve Romano, senior vice president, head of Medicines Development Group for Global Innovative Pharmaceuticals, Pfizer Inc.

About the Clinical Trial Program

AMPLIFY

As described in the SmPC, in the AMPLIFY study a total of 5,395 patients were randomized to treatment with *Eliquis* 10 mg twice daily orally for seven days followed by *Eliquis* 5 mg twice daily orally for six months, or enoxaparin 1 mg/kg twice daily subcutaneously for at least five days (until INR? 2) and warfarin (target INR range 2.0-3.0) orally for six months.

The mean age was 56.9 years and 89.8 percent of randomized patients had unprovoked VTE events.

In the study, *Eliquis* was shown to be non-inferior to enoxaparin/warfarin in the combined primary endpoint of adjudicated recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related death.

Eliquis efficacy in initial treatment of VTE was consistent between patients who were treated for a PE [Relative Risk 0.9; 95 percent CI (0.5, 1.6)] or DVT [Relative Risk 0.8; 95 percent CI (0.5, 1.3)]. Efficacy across subgroups, including age, gender, body mass index (BMI), renal function, extent of index PE, location of DVT thrombus, and prior parenteral heparin use was generally consistent.

For patients randomized to warfarin, the mean percentage of time in therapeutic range (TTR) (INR 2.0-3.0) was 60.9. The effect of *Eliquis* on recurrent symptomatic VTE or VTE- related death was consistent across the different levels of center TTR; within the highest quartile of TTR according to center, the relative risk for *Eliquis* vs enoxaparin/warfarin was 0.79 (95 percent CI, 0.39, 1.61).

The primary safety endpoint was major bleeding. In the study, *Eliquis* was statistically superior to enoxaparin/warfarin in the primary safety endpoint [Relative Risk 0.31, 95 percent confidence interval (0.17, 0.55), P-value <0.0001].

The adjudicated major bleeding and clinically relevant non-major (CRNM) bleeding at any anatomical site were generally lower in the *Eliquis* group as compared to the enoxaparin/warfarin group. Adjudicated International Society on Thrombosis and Haemostasis (ISTH) major gastrointestinal bleeding occurred in 6 (0.2 percent) *Eliquis*-treated patients and 17 (0.6 percent) enoxaparin/warfarin-treated patients.

AMPLIFY- EXT

As described in the SmPC, in the AMPLIFY-EXT study a total of 2,482 patients were randomized to treatment with *Eliquis* 2.5 mg twice daily orally,*Eliquis* 5 mg twice daily orally, or placebo for 12 months after completing six to 12 months of initial anticoagulant treatment. Of these, 836 patients (33.7 percent) participated in the AMPLIFY study prior to enrollment in the AMPLIFY-EXT study.

The mean age was 56.7 years and 91.7 percent of randomized patients had unprovoked VTE events.

In the study, both doses of *Eliquis* were statistically superior to placebo in the primary endpoint of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause death.

Eliquis efficacy for prevention of a recurrence of a VTE was maintained across subgroups, including age, gender, BMI, and renal function.

The primary safety endpoint was major bleeding during the treatment period. In the study, the incidence in major bleeding for both *Eliquis* doses was not statistically different from placebo. There was no statistically significant difference in the incidence of major, clinically relevant non-major, minor, and all bleeding between the *Eliquis* 2.5 mg twice daily and placebo treatment groups. The recommended dose of *Eliquis* for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily.

Adjudicated ISTH major gastrointestinal bleeding occurred in 1 (0.1 percent) *Eliquis*-treated patient at the 5 mg twice daily dose, no patients at the 2.5 mg twice daily dose, and 1 (0.1 percent) placebo-treated patient.

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 adult patients with NVAF in the United States, European Union, Japan and a number of other countries around the world. *Eliquis* is approved for the prophylaxis 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 in the European Union. *Eliquis* is not approved for this indication in the United States.

IMPORTANT SAFETY INFORMATION FROM U.S. PRESCRIBING INFORMATION

WARNINGS: (A) DISCONTINUING ELIQUIS IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA

(A) Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered.

(B) When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins, heparinoids, or Factor Xa inhibitors for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet aggregation inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Monitor patients for signs and symptoms of neurologic impairment. If neurologic compromise is noted, urgent treatment is necessary. Consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- **Increased Risk of Stroke with Discontinuation of ELIQUIS in Patients with Nonvalvular Atrial Fibrillation:** Discontinuing 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 patients with nonvalvular atrial fibrillation. If ELIQUIS must be discontinued for a reason other than pathological bleeding, 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. Patients should be made aware of signs or symptoms of blood loss and instructed to immediately report 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. Hemodialysis does not appear to have a substantial impact on apixaban exposure. Protamine sulfate and vitamin K would not be expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated charcoal reduces absorption of apixaban thereby lowering apixaban plasma concentrations.
- **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.

ADVERSE REACTIONS

The most common and most serious adverse reactions reported with ELIQUIS (apixaban) 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 5 mg twice daily, the dose of ELIQUIS should be decreased when it 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 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.
- **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

Venous thromboembolism, or VTE, encompasses two serious conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is a blood clot in a vein, usually in the lower leg, thigh, or pelvis, which partially or totally blocks the flow of blood. PE is a blood clot blocking one or more vessels in the lungs. DVT causes multiple symptoms including pain, swelling, and redness, and more importantly, can progress to PE, which carries the risk of sudden death. Approximately one million patients in the EU are diagnosed every year with VTE.

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.

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. Among other risks, there can be no guarantee that the

approval of these additional indications in Europe will lead to increased commercial success or that Eliquis will be approved for these additional indications in the U.S. or in other countries. 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, 2013, 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 July 29, 2014. 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's (apixaban's) potential benefits and about additional indications for Eliquis in the EU for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and the prevention of recurrent DVT and PE in adults 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 regarding the commercial success of the additional indications in the EU; whether and when the FDA or regulatory authorities in other jurisdictions will approve applications for these potential additional indications, as well as their decisions regarding labeling and other matters that could affect the availability or commercial potential of such potential additional indications;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, 2013 and in our subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information 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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