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Eliquis® (apixaban) Receives CHMP Positive Opinion for the Treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), and Prevention of Recurrent DVT and PE

Friday, June 27, 2014 - 03:00am

Bristol-Myers Squibb Company (NYSE:BMY) and Pfizer Inc. (NYSE:PFE) today announced that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has adopted a positive opinion recommending that *Eliquis* (apixaban) be granted marketing authorization for the treatment of DVT (deep vein thrombosis) and PE (pulmonary embolism), and the prevention of recurrent DVT and PE, in adults. The CHMP's positive opinion will now be reviewed by the European Commission (EC). The decision on whether to approve *Eliquis* for this indication will be made by the EC and will be applicable to all European Union member states plus Iceland and Norway.

The positive opinion was based on the results from the pivotal AMPLIFY and AMPLIFY-EXT studies. 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**), a randomized, double-blind, multicenter trial, included 5,395 patients (2,691 were randomized to *Eliquis* and 2,704 were randomized to standard of care, which was initial enoxaparin treatment overlapped by warfarin therapy) with confirmed symptomatic DVT or PE requiring treatment for six months, and evaluated *Eliquis* therapy compared to standard of care. The primary efficacy endpoint was the composite endpoint of recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related death. The primary safety endpoint was the incidence of major bleeding compared to standard of care.

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), a randomized, double-blind, multicenter trial, included 2,486 patients (842 were randomized to *Eliquis* 2.5 mg, 815 were randomized to *Eliquis* 5 mg and 829 were randomized to placebo) with prior VTE who had completed six to 12 months of anticoagulation treatment for DVT or PE, and evaluated *Eliquis* therapy compared to placebo. The primary efficacy endpoint was reduction of the composite of symptomatic, recurrent VTE and death from any cause. The primary safety endpoint was the incidence of major bleeding.

IMPORTANT SAFETY INFORMATION

**WARNINGS: (A) DISCONTINUING ELIQUIS IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLAT
CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATO**

**(A) Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke
of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS mu
pathological bleeding, coverage with another anticoagulant should be strongly considered.**

**(B) When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulate
low molecular weight heparins, heparinoids, or Factor Xa inhibitors for prevention of thromboembolic complicat
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 analge
affecting hemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet aggregation inhibitors, or c
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 tr
potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for t**

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), 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 pulmonary embolism (PE), a blood clot that blocks one or more vessels in the lungs.[1] Approximately one million patients in the EU are diagnosed every year with VTE.[2] In the US, the number of adults with VTE is projected to more than double from 0.95 million in 2006 to 1.82 million in 2050.[3] Once a VTE has occurred, up to 10 percent of people may have a VTE reoccurrence, which could potentially be fatal. [4]

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 the prophylaxis of DVT which can lead to PE 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.

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 Eliquis will receive approval for these additional indications or, if approved, that these additional indications will lead to increased commercial success. 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 June 27, 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 that involves substantial risks and uncertainties about Eliquis's (apixaban's) potential benefits and about potential 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 (the "potential additional indications"). Such risks and uncertainties include, among other things, (i) whether and when the European Commission (the "EC") may approve the marketing authorization application for the potential additional indications, as well as the EC's decisions regarding labeling and other matters that could affect the availability or commercial potential of the potential additional indications; (ii) the uncertainties regarding the commercial success of the potential additional indications in the EU; and (iii) 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 its subsequent reports on Form 10-Q and Form 8-K.

[1] Deep Vein Thrombosis (DVT) / Pulmonary Embolism (PE) - Blood Clot Forming in a Vein. Centers for Disease Control and Prevention. 25 September, 2012. Available at: http://www.cdc.gov/ncbddd/dvt/facts.html. Accessed February 20, 2014.

[2] Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb.Haemost. 2007;98,(4)756-764.

[3] Deitelzweig SB, Johnson BH, Lin J, et al. Prevalence of clinical venous thromboembolism in the USA: Current trends and future projections. Am J Hematol. 2011; 86(2):217-220.

[4] Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. Arch Intern Med. 2010;170:1710–1716.

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