Bristol-Myers Squibb and Pfizer Sign Collaboration with Portola Pharmaceuticals to Develop and Commercialize Investigational Andexanet Alfa in Japan

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PRINCETON, N.J. & NEW YORK--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) and Pfizer Inc. (NSYE:PFE) today announced that the companies have entered into a collaboration agreement with Portola Pharmaceuticals Inc. (Nasdaq: PTLA) to develop and commercialize the investigational agent andexanet alfa in Japan. Andexanet alfa, which is in Phase 3 clinical development in the U.S. and Europe, is designed to reverse the anticoagulant activity of Factor Xa inhibitors, includingEliquis (apixaban).

“We are committed to reducing the risk of stroke in nonvalvular atrial fibrillation patients and treating deep vein thrombosis and pulmonary embolism,” said Douglas Manion, M.D., head of Specialty Development, Bristol-Myers Squibb. “Bristol-Myers Squibb and Pfizer’s agreement with Portola is an important step forward toward the goal of delivering the first reversal agent for Factor Xa inhibitors, including Eliquis, to patients in Japan. The ability to reverse the anticoagulation effect of Eliquis and other Factor Xa inhibitors may be helpful for some patients who experience a major bleeding event or require emergency surgery while onEliquis or another Factor Xa inhibitor.”

“This agreement in Japan is another great example of the alliance’s commitment to the patients we serve. Eliquis has proven to be an important treatment option for patients at risk for stroke and blood clots due to nonvalvular atrial fibrillation and for the treatment

of deep vein thrombosis and pulmonary embolism, but currently there is no approved reversal agent," said Rory O'Connor, M.D., senior vice president and head of Global Medical Affairs, Global Innovative Pharmaceuticals Business, Pfizer Inc. "With our partner, Bristol-Myers Squibb, we look forward to working with Portola to develop andexanet alfa as a reversal agent for Eliquis in Japan."

Under the terms of the agreement, Portola will receive an upfront payment of $15 million, potential regulatory milestones of $20 million and sales-based milestones of $70 million as well as compensation based on andexanet alfa net sales. Bristol-Myers Squibb and Pfizer will co-fund with Portola the development and commercialization of andexanet alfa in Japan. Portola will retain rights to andexanet alfa outside of Japan and remain responsible for the manufacturing supply.

This agreement builds on the companies' existing clinical collaboration to develop andexanet alfa in the U.S. and Europe. In December 2015, Portola announced it had completed the submission of a Biologics License Application to the U.S. Food and Drug Administration (FDA) for andexanet alfa and was awaiting acceptance for filing. The FDA assigned a PDUFA date of August 17, 2016, under an Accelerated Approval pathway. Portola has stated that it plans to submit an EU application in 2017.

About Andexanet Alfa

Andexanet alfa, an investigational drug, is a modified human Factor Xa molecule that acts as a decoy to target and sequester with high specificity both oral and injectable Factor Xa inhibitors in the blood. Once bound, the Factor Xa inhibitors are unable to bind to and inhibit native Factor Xa, thus allowing for the restoration of normal hemostatic processes. Andexanet alfa is the only compound being studied as a reversal agent for Factor Xa inhibitors that directly and specifically corrects anti-Factor Xa activity – the anticoagulant mechanism of these agents.

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 thus blood clot formation. Eliquis is a prescription medicine approved for multiple indications in the United States, the European Union (which includes 28 member states plus Iceland and Norway) and Japan, as well as a number of other countries around the world based on efficacy and safety data, including results from seven Phase 3 clinical trials. In Japan, Eliquis is approved for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF). Eliquis is also approved in Japan for the

treatment of venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE following initial therapy.

ELIQUIS Important Safety Information and Indications

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 Prescribing Information, including BOXED WARNINGS and Medication Guide, available at www.bms.com.

Indications in the United States

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.

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 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.

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 the research, development and commercialization of pharmaceutical products. 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, the compound described in this release is subject to all the risks inherent in the drug development process, and there can be no assurance that the development of this compound will be successful. Forward-looking statements in the 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, 2014, its Quarterly Reports on Form 10-Q, and 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 February 1, 2016. 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) and andexanet alfa, including their 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 data and additional analyses of existing clinical data; whether and when any Biologics License Application (BLA) may be filed for andexanet alfa; whether and when regulatory authorities will approve any such BLA; decisions by regulatory authorities regarding label and andexanet alfa; 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, 2014 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.

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