Portola Pharmaceuticals Presents New In Vitro Data Demonstrating that Four-Factor Prothrombin Complex Concentrates (4F-PCCs) Had No Direct Effect on Inhibition of Thrombin Generation by Factor Xa Inhibitors

July 8, 2019

- Data Presented at the Annual Congress of the International Society on Thrombosis and Haemostasis (ISTH 2019) -

SOUTH SAN FRANCISCO, Calif., July 8, 2019 /PRNewswire/ -- Portola Pharmaceuticals, Inc.® (Nasdaq: PTLA) today announced new *invitro* data establishing the relationship between concentrations of the direct oral anticoagulants (DOACs) apixaban and rivaroxaban and the ability of four-factor prothrombin complex concentrate (4F-PCC) to correct inhibition of thrombin generation, compared with warfarin anticoagulation reversal by 4F-PCC. Data were presented on July 8, 2019 during a poster session at the Annual Congress of the International Society on Thrombosis and Haemostasis (ISTH 2019) in Melbourne, Australia.

Results showed that, while effective in reversing inhibition of thrombin generation in plasma from patients treated with warfarin, 4F-PCCs did not appear to have an effect on the inhibition of thrombin generation by apixaban or rivaroxaban unless the Factor Xa inhibitor concentration was less than 75 ng/mL. In contrast, data from the same thrombin generation assay demonstrated that Andexxa® [coagulation factor Xa (recombinant), inactivated-zhzo] fully corrected the inhibition of thrombin generation by apixaban and rivaroxaban across a broad range of inhibitor concentrations.

"The results of this new *in vitro* study provide further evidence as to why 4F-PCCs are not currently indicated or approved for the reversal of Factor Xa activity in patients treated with apixaban and rivaroxaban," said Pamela Conley, Ph.D., senior vice president of research at Portola Pharmaceuticals. "While our study results further support the efficacy of 4F-PCCs in reversing the anticoagulant effects of warfarin, they appear to have minimal impact on the inhibition of thrombin generation by direct Factor Xa inhibitors over the range of exposures typically seen in bleeding patients. For example, in the ANNEXA-4 trial of Andexxa in Factor Xa inhibitor-treated patients with acute major bleeding, approximately 75% of the patients had anticoagulant concentrations above 75 ng/mL at the time of Andexxa reversal therapy."

In this study, tissue factor (TF)-initiated thrombin generation was assessed using plasma from healthy donors or patients treated with warfarin. Reversal of warfarin anticoagulation by 4F-PCC (using commercially available Kcentra®/Beriplex®) was performed using individual plasma samples from warfarin-treated patients to which the equivalent of either the low or high therapeutic 4F-PCC dose was added. Reversal of apixaban or rivaroxaban anticoagulation by 4F-PCC and Andexxa was similarly measured using normal human plasma containing different concentrations of Factor Xa inhibitor (0-250 ng/mL for rivaroxaban and 0-125 ng/mL for apixaban). Finally, the effect of individual purified plasma components of 4F-PCC on thrombin generation in normal plasma was measured.

"These data demonstrate that 4F-PCCs are likely not to be effective in reversing DOAC concentrations over 75 ng/mL and underscore the need for Andexxa, a unique reversal agent designed specifically to reverse Factor Xa inhibitor activity in apixaban- or rivaroxaban-treated patients experiencing a life-threatening bleed," said Scott Garland, president and chief executive officer of Portola. "Andexxa is now recognized by 16 U.S. and European medical society guidelines and we look forward to continuing to generate additional data that further characterizes the efficacy and safety profile of Andexxa. Our hope is that this ongoing research will assist in ensuring that physicians have the information they need to appropriately treat life-threatening bleeds associated with Factor Xa inhibitor use."

The use of Factor Xa inhibitors is rapidly growing because of their efficacy and safety profile compared to warfarin and enoxaparin in preventing and treating thromboembolic conditions such as stroke, pulmonary embolism and venous thromboembolism (VTE). This growth has come with a related increase in the incidence of hospital admissions and deaths related to bleeding, the major complication of anticoagulation. In the U.S. alone in 2017, there were approximately 140,000 hospital admissions attributable to Factor Xa inhibitor-related bleeding.

Andexxa is the first and only reversal agent approved for adult patients treated with the Factor Xa inhibitors apixaban or rivaroxaban when reversal of

anticoagulation is needed due to life-threatening or uncontrolled bleeding. It received both Orphan Drug and Breakthrough Therapy designations from the U.S. Food and Drug Administration (FDA), and it was approved on May 3, 2018, under the FDA's Accelerated Approval pathway. It is marketed in Europe as Ondexxya® (andexanet alfa).

IMPORTANT SAFETY INFORMATION FOR ANDEXXA [coagulation factor Xa (recombinant), inactivated-zhzo]

BOXED WARNING: THROMBOEMBOLIC RISKS, ISCHEMIC RISKS, CARDIAC ARREST AND SUDDEN DEATHS

See full prescribing information for complete boxed warning

Treatment with Andexxa has been associated with serious and life-threatening adverse events, including:

- **Arterial and venous thromboembolic events**
- **Ischemic events, including myocardial infarction and ischemic stroke**
- **Cardiac arrest**
- **Sudden deaths**

Monitor for thromboembolic events and initiate anticoagulation when medically appropriate. Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.

Indication
Andexxa [coagulation factor Xa (recombinant), inactivated-zhzo] is a recombinant modified human Factor Xa (FXa) protein indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

This indication is approved under accelerated approval based on the change from baseline in anti-FXa activity in healthy volunteers. An improvement in hemostasis has not been established. Continued approval for this indication may be contingent upon the results of studies to demonstrate an improvement in hemostasis in patients.

Limitation of Use
Andexxa has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any FXa inhibitors other than apixaban or rivaroxaban.

SELECT IMPORTANT SAFETY INFORMATION

Thromboembolic and Ischemic Risk

The thromboembolic and ischemic risks were assessed in 185 patients who received the Generation 1 product and in 124 patients who received the Generation 2 product. The median time to first event was six days, and patients were observed for these events for 30 days following Andexxa infusion. Of the 86 patients who received Generation 1 product and were re-anticoagulated prior to a thrombotic event, 11 (12.7%) patients experienced a thromboembolic event, ischemic event, cardiac event or death.

Monitor patients treated with Andexxa for signs and symptoms of arterial and venous thromboembolic events, ischemic events, and cardiac arrest. To reduce thromboembolic risk, resume anticoagulant therapy as soon as medically appropriate following treatment with Andexxa.

The safety of Andexxa has not been evaluated in patients who experienced thromboembolic events or disseminated intravascular coagulation within two weeks prior to the life-threatening bleeding event requiring treatment with Andexxa. Safety of Andexxa also has not been evaluated in patients who received prothrombin complex concentrates, recombinant Factor VIIa, or whole blood products within seven days prior to the bleeding event.

Re-elevation or Incomplete Reversal of Anti-FXa Activity
The time course of anti-FXa activity following Andexxa administration was consistent among the healthy volunteer studies and the ANNEXA-4 study in bleeding patients. Compared to baseline, there was a rapid and substantial decrease in anti-FXa activity corresponding to the Andexxa bolus. This decrease was sustained through the end of the Andexxa continuous infusion. The anti-FXa activity returned to the placebo levels approximately two hours after completion of a bolus or continuous infusion. Subsequently, the anti-FXa activity decreased at a rate similar to the clearance of the FXa inhibitors.

Thirty-eight patients who received the Generation 1 product were anticoagulated with apixaban and had baseline levels of anti-FXa activity > 150 ng/mL. Nineteen of these 38 (50%) patients experienced a > 93% decrease from baseline anti-FXa activity after administration of Andexxa. Eleven patients who were anticoagulated with rivaroxaban had baseline anti-FXa activity levels > 300 ng/mL. Five of the 11 patients experienced a > 90% decrease from baseline anti-FXa activity after administration of Andexxa. Anti-FXa activity levels for patients who received the Generation 2 product were not available.

Adverse Reactions
The most common adverse reactions (≥ 5%) in patients receiving Andexxa were urinary tract infections and pneumonia.

The most common adverse reactions (≥ 3%) in healthy volunteers treated with Andexxa were infusion-related reactions.

Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. Using an electrochemiluminescence (ECL)-based assay, 145 Generation 1 Andexxa-treated healthy subjects were tested for antibodies to Andexxa as well as antibodies cross-reacting with Factor X (FX) and FXa. Low titers of anti-Andexxa antibodies were observed in 26/145 healthy subjects (17%); 6% (9/145) were first observed at Day 30 with 20 subjects (14%) still having titers at the last time point (days 44 to 48). To date, the pattern of antibody response in patients in the ANNEXA-4 study has been similar to that observed in healthy volunteers with 6% (6/98) of the patients having antibodies against Andexxa. None of these anti-Andexxa antibodies were neutralizing. No antibodies cross-reacting with FX or FXa were detected in healthy subjects (0/145) or in bleeding patients (0/98) to date. There is insufficient data to assess for the presence of anti-Andexxa antibodies for subjects received the Generation 2 product.

About Portola Pharmaceuticals, Inc.
Portola Pharmaceuticals is a global, commercial-stage biopharmaceutical company focused on the discovery, development and commercialization of novel therapeutics that could significantly advance the fields of thrombosis and other hematologic conditions. The Company's first two commercialized products are Andexxa® [coagulation factor Xa (recombinant), inactivated-zhzo], marketed in Europe as Ondexxya® (andexanet alfa), and Bevyxxa® (betrixaban). The company also is advancing cerdulatinib, a SYK/JAK inhibitor being developed for the treatment of hematologic cancers. Founded in 2003 in South San Francisco, California, Portola has operations in the United States and Europe.

Forward-Looking Statements
Statements contained in this press release regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to: the potential of Andexxa to address life-threatening bleeding associated with the use of the Factor Xa inhibitors apixaban or rivaroxaban, clinical treatment of patients and the need for a specific Factor Xa inhibitor reversal agent. These statements are subject to significant risks and uncertainties, and actual results could differ materially from those projected. These risks and uncertainties include, without limitation, the risk that physicians, patients and payers may not see the benefits of utilizing Andexxa; the possibility of unfavorable results from additional clinical trials involving Andexxa; the risk that reimbursement limitations may have significant limitations on its use; the risk that we may not obtain additional regulatory approvals necessary to expand approved indications for Andexxa; our ability to establish commercial operations in Europe and generate product revenue within projected timelines and budget; our expectation that we will incur losses for the foreseeable future and will need additional funds to finance our operations; the accuracy of our estimates regarding expenses and capital requirements; our ability to successfully build a hospital-based sales force and commercial infrastructure; our ability to obtain and maintain intellectual property protection for our product candidates; and our ability to retain key scientific or management personnel. These and other risks and uncertainties are described more fully in our most recent filings with the Securities and Exchange Commission, including our most recent annual report on Form 10-Q. All forward-looking statements contained in this press release speak only as of the date on which they were made. We undertake no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

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