Portola Pharmaceuticals Announces New Analysis from the ANNEXA-4 Study of its Factor Xa Inhibitor Reversal Agent Andexxa® in Patients with Spontaneous (Non-Traumatic) Intracranial Hemorrhage

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– Excellent or Good Hemostasis Achieved in 79% of Evaluable Patients with Spontaneous Intracranial Hemorrhage –

– Data Featured in an Oral Presentation at the 5th European Stroke Organisation Conference –

SOUTH SAN FRANCISCO, Calif., May 22, 2019 (GLOBE NEWSWIRE) -- Portola Pharmaceuticals, Inc.® (Nasdaq: PTLA) today announced the presentation of a new analysis of data from an important subgroup of ANNEXA-4, the Company's Phase 3b/4 trial of its Factor Xa inhibitor antidote Andexxa® [coagulation factor Xa (recombinant), inactivated-zhzo] in patients with acute major bleeding while taking a Factor Xa inhibitor. Data on a key subset of patients with spontaneous (non-traumatic) intracranial hemorrhage are being featured in an oral presentation today at the 5th European Stroke Organisation Conference (ESOC 2019) in Milan, Italy.

Spontaneous intracranial hemorrhage is a bleeding event in the brain not caused by trauma, and it is associated with high rates of mortality and morbidity. Among the 352 patients in the ANNEXA-4 study, 227 (64%) experienced an intracranial hemorrhage. Of these,128 (56%) were treated for a spontaneous intracranial hemorrhage, 98 of which were evaluable for hemostatic efficacy. Among this subset, 79% (n=77/98) achieved excellent or good hemostasis (stoppage of bleeding) over the 12-hour period following treatment with Andexxa, as determined by an independent adjudication committee. This is consistent with the 82% (n=204/249) reported in the full ANNEXA-4 study across patients with all types of bleeds (e.g., intracranial hemorrhage bleeds, gastrointestinal and other compartmental bleeds).

Among the 98 efficacy evaluable patients in this subset, the median increase in hematoma volume from baseline to 12 hours was 0.06 milliliters, a volume increase of 1% over baseline. Further, 71 patients in this subset experienced a spontaneous, single-compartment, intracerebral hemorrhage, a bleed type that allows for the most precise measurement of hematoma volume. Of the patients that achieved excellent or good hemostatic efficacy within one hour post Andexxa, 98% (n=55/56) maintained excellent or good hemostatic control 12 hours following Andexxa administration.

Within 30 days of enrollment, thrombotic events occurred in 14 patients with spontaneous intracranial hemorrhage (10.9%) and death occurred in 24 patients (18.8%), consistent with the full ANNEXA-4 study results and the high background thrombotic risk of the enrolled patient population. Among the 18 patients who re-started oral anticoagulation therapy within 30 days, no thrombotic events were observed. The majority of thrombotic events occurred in patients who delayed or did not re-start anticoagulation therapy with a Factor Xa inhibitor during the follow-up period.

"A spontaneous intracranial hemorrhage while on a Factor Xa inhibitor is a significant challenge that can result in death, and for which there traditionally have been no direct pharmacologic treatment options," said Andrew M. Demchuk, M.D., FRCPC, director of the Calgary Stroke Program at the University of Calgary. "These data demonstrate that, even in this difficult-to-treat subset of patients, the hemostatic efficacy and safety of Andexxa is compelling and consistent. Additionally, there were no observed thrombotic events after resumption of oral anticoagulation when it was possible."

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

"These data help to further characterize the durable hemostatic efficacy of Andexxa regardless of age, dose, type of Factor Xa inhibitor and type of bleed, and we look forward to continuing to generate additional data that highlight Andexxa's safety and efficacy profile," said Scott Garland, Portola's president and chief executive officer. "We have a significant opportunity to impact patient lives, and we are working as fast as we can to ensure patients in the U.S. and Europe have access to this potentially life-saving medicine."

Andexxa received both U.S. Orphan Drug and U.S. Food and Drug Administration (FDA) Breakthrough Therapy designations and was approved on May 3, 2018 under the FDA's Accelerated Approval pathway. It received conditional marketing authorization from the European Commission on April 26, 2019, and will be marketed in Europe as Ondexxya® (andexanet alfa). It is the first and only antidote indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

ANNEXA-4 Study Design

ANNEXA-4 is a global, prospective, single-arm, open-label clinical trial designed to evaluate andexanet alfa in patients who present with an acute

major bleed while receiving apixaban, rivaroxaban, edoxaban or enoxaparin. This multi-center cohort study was not randomized and all participants received andexanet alfa given as a bolus dose over 20-30 minutes followed by a two-hour (120 minute) infusion. Patients received a low or high dose infusion depending on which Factor Xa inhibitor they received and the time since they received the last dose. Patients were evaluated for 30 days following andexanet alfa administration. The co-primary efficacy endpoints are the maximum percent reduction in anti-Factor Xa activity and assessment of hemostasis over 12 hours following the infusion. Hemostatic efficacy was assessed by an independent endpoint adjudication committee using predetermined criteria as either excellent, good or poor/none. The primary safety endpoints were mortality and thrombotic events at 30 days, and the development of antibodies to Andexxa or to native Factor X and Factor Xa.

Among the 227 patients in the ANNEXA-4 trial who experienced an intracranial hemorrhage, 99 (44%) experienced a traumatic intracranial bleed and 128 (56%) experienced a spontaneous (non-traumatic) intracranial bleed. There are four basic anatomic types of intracranial bleeds: 1) intracerebral (within the brain tissue itself); 2) intraventricular (in the hollow cavities in the center of the brain that contain spinal fluid); 3) subdural (under the outer lining of the brain); and 4) subarachnoid (under the inner lining of the brain). The bleeding can be confined to any one of these four types or, occasionally, occurs in combination.

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, the need for a specific Factor Xa inhibitor reversal agent, the number of patients who could potentially benefit from Andexxa and our plans to launch Ondexxya in Europe. 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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