U.S. Food and Drug Administration Approves Portola Pharmaceuticals' Prior Approval Supplement for Andexxa® Generation 2 Manufacturing Process

December 31, 2018

– Expands Patient Access to Andexxa, the First and Only Antidote for Reversal of the Factor Xa Inhibitors Rivaroxaban or Apixaban –

– Full Commercial Launch to Begin January 2019 –

SOUTH SAN FRANCISCO, Calif., Dec. 31, 2018 (GLOBE NEWSWIRE) -- Portola Pharmaceuticals, Inc.® (Nasdaq: PTLA) today announced that the U.S. Food and Drug Administration (FDA) has approved the Company's Prior Approval Supplement (PAS) for its large-scale, second generation Andexxa® [coagulation factor Xa (recombinant), inactivated-zhzo], allowing for broad commercial launch in the United States.

Andexxa received both U.S. Orphan Drug and FDA Breakthrough Therapy designations and was initially approved on May 3, 2018 under the FDA's Accelerated Approval pathway. 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.

"It is clear from the response to the Andexxa Early Supply Program that there is significant need for a specific reversal agent that can address life-threatening bleeding associated with the use of the Factor Xa inhibitors apixaban and rivaroxaban," said Scott Garland, Portola's president and chief executive officer. "We are pleased to now be able to stock hospitals nationwide and serve all patients in the U.S. who could benefit from the potential life-saving impact of Andexxa."

The use of Factor Xa inhibitors is rapidly growing because of their efficacy and safety profile compared to enoxaparin and warfarin 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.

The Company will provide additional details on the commercial launch plans for Andexxa during its annual corporate webcast scheduled for Tuesday, January 8, at 7:00 a.m. PT (10:00 a.m. ET). The live webcast will be available on the Company's website at www.portola.com.

IMPORTANT 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.

Detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Andexxa with the incidence of antibodies to other products may be misleading.

About Portola Pharmaceuticals, Inc.
Portola Pharmaceuticals is a 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 diseases. The Company's two FDA-approved medicines are Andexxa® [coagulation factor Xa (recombinant), inactivated-zhzo], the first and only antidote for patients treated with rivaroxaban and apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding, and Bevyxxa® (betrixaban), the first and only oral, once-daily Factor Xa inhibitor for the prevention of VTE in adult patients hospitalized for an acute medical illness. The company also is advancing cerdulatinib, a Syk/JAK inhibitor for the treatment of hematologic cancers.

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, our intention to conduct a broad commercial launch of Andexxa in the United States and increase patient access to Andexxa. Risks that contribute to the uncertain nature of the forward-looking statements include: the risk that physicians, patients and payers may not see the benefits of utilizing Andexxa or Bevyxxa for the indications which they are approved; our ability to continue to manufacture our products and to expand approved manufacturing facilities; the possibility of unfavorable results from additional clinical trials involving Andexxa; the risk that the EMA may not approve Andexxa in the currently anticipated timelines or at all, and that any marketing approvals or 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 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 quarterly 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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