Portola Investor Room

Andexxa Highlighted as a First-Line Factor Xa Reversal Option by the American College of Emergency Physicians

- Recommendations from Multidisciplinary Expert Panel on Anticoagulant Reversal and Replacement Guidance Published in Annals of Emergency Medicine -

SOUTH SAN FRANCISCO, Calif., Nov. 15, 2019 /PRNewswire/ -- Portola Pharmaceuticals, Inc.® (NASDAQ: PTLA) today announced that *Annals of Emergency Medicine*, the journal of the American College of Emergency Physicians (ACEP), published a multidisciplinary anticoagulant reversal and replacement guidance statement. The guidance statement is supported by literature and consensus definitions to support evaluation and treatment of the bleeding and nonbleeding patient requiring emergency invasive procedures.

In the guidance statement, ACEP highlighted Andexxa® [coagulation factor Xa (recombinant), inactivated-zhzo] as a first-in-line, U.S. Food and Drug Administration (FDA) approved reversal agent for patients treated with apixaban or rivaroxaban, as compared to 4F-PCC, which are highlighted as a second-in-line option for Factor Xa reversal and recommended for use only if Andexxa is not available.

"As the number of patients taking Factor Xa inhibitors continues to grow, it is encouraging that many societies, now including ACEP, have officially recognized the importance of specific, rapid anticoagulation reversal when life-threatening bleeding occurs," said leading author Christoper W. Baugh, M.D., M.B.A., Department of Emergency Medicine, Brigham and Women's Hospital, Boston, MA. "This new guidance aligns with clinical practice at our institution, where we are seeing positive clinical outcomes in patients treated with Andexxa."

A multidisciplinary expert panel of academic and community physicians defined the consensus recommendations through the creation and interpretation of a consensus anticoagulation reversal or replacement decision tree and stepwise guidance framework to aid the emergency physician's evaluation and management of the bleeding patient receiving an anticoagulant. The expert panel also reached agreement on key definitions of life-threatening bleeding, bleeding at a critical site, and emergency surgery or urgent invasive procedure to support decision tree interpretation.

"This guidance further exemplifies the breakthrough innovation of Andexxa and the clinical value of rapidly reversing the anticoagulant effects of Factor Xa inhibitors rivaroxaban or apixaban in the event of life-threatening or uncontrolled bleeding," said Scott Garland, Portola's president and chief executive officer. "We are encouraged by ACEP's characterization of Andexxa as a Tier 1 recommendation 'most aligned with FDA-approved indications and the highest quality of evidence supporting their use' as it highlights its potential to benefit thousands of patients facing life-threatening bleeding associated with the use of rivaroxaban or apixaban."

The consensus statement is available for reference here: https://www.annemergmed.com/article/S0196-

0644(19)31181-3/fulltext.

About Factor Xa Inhibitor-Related Bleeding

The use of Factor Xa inhibitors is growing rapidly 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 2017, there were approximately 150,000 hospital admissions attributable to Factor Xa inhibitor-related bleeding and approximately 2,100 bleeding-related deaths per month in the U.S.

About Andexxa

Andexxa is a recombinant protein specifically designed to bind to Factor Xa inhibitors and rapidly reverse their anticoagulant effect. Andexxa was approved by the FDA in May 2018 as the first and only antidote indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Andexxa received both U.S. Orphan Drug and FDA Breakthrough Therapy designations and was approved under the FDA's Accelerated Approval pathway based on the change from baseline in anti-Factor Xa activity in healthy volunteers.

For additional Important Safety Information and Andexxa's full Prescribing Information, please visit http://www.Andexxa.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 indicated for patients treated with rivaroxaban and 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-Factor Xa (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.

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 and rivaroxaban.

SELECT IMPORTANT SAFETY INFORMATION

Thromboembolic Risk
Arterial and venous thromboembolic events, ischemic events, sudden deaths, or events where a thrombotic event could not be ruled out were observed within 30 days post- Andexxa administration in 33 of the 185 patients (17.8%) evaluable for safety in the ongoing ANNEXA-4 study. The median time to these events was six days. Of the 86 patients who 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. No thromboembolic events were observed in 223 healthy volunteers who received Factor Xa inhibitors and were treated 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. Following the infusion, there was an increase in anti-FXa activity, which peaked four hours after infusion in ANNEXA-4 subjects. After this peak, the anti-FXa activity decreased at a rate similar to the clearance of the FXa inhibitors.

Thirty-eight patients who were anticoagulated with apixaban 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.

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. 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% of the patients having antibodies against Andexxa (6/98 patients). 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 to date (0/98).

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, statements regarding projected growth in the addressable patient population for Andexanet and the potential benefit of 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 for the indications for which it is 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; our ability to grow our commercial operations in the EU and generate product revenue within projected timelines and budget; the risk that we may not obtain additional regulatory approvals necessary to expand or maintain 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; our ability to retain key scientific or management personnel and general market conditions. 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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