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Vertex Receives European CHMP Positive Opinion for KALYDECO™ (ivacaftor) in Eight Non-G551D Gating Mutations

-In Europe, approximately 250 people ages 6 and older have one of 8 additional gating mutations-

-KALYDECO is the first medicine to treat the underlying cause of CF in people with non-G551D gating mutations-

EYSINS, Switzerland--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced that the European Committee for Medicinal Products for Human Use (CHMP) has issued a positive opinion recommending the approval of KALYDECO™ (ivacaftor) for people with cystic fibrosis (CF) ages 6 and older who have one of eight non-G551D gating mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. KALYDECO was first approved in Europe in July 2012 for people with CF ages 6 and older who have at least one copy of the G551D mutation, which is the most common gating mutation. The eight additional gating mutations included in today's recommendation are: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D. In Europe, approximately 250 people ages 6 and older have one of these non-G551D gating mutations.

"People with these additional gating mutations generally have severe cystic fibrosis, similar to patients with the most common gating mutation, G551D. There is an urgent need for new medicines that address the underlying cause of the disease for people with these mutations," said Jeffrey Chodakewitz, M.D., Senior Vice President and Chief Medical Officer at Vertex. "Today's recommendation for the use of ivacaftor in people with eight additional gating mutations represents an important step toward our goal of helping more people with CF."

Cystic fibrosis is caused by a defective or missing CFTR protein that results from mutations in the *CFTR* gene. CFTR proteins act as channels at the cell surface that control the flow of salt and water into and out of the cell. In people with gating mutations, the CFTR protein at the cell surface is defective and does not work properly, causing abnormally thick, sticky mucus to build up in the lungs. The digestive tract and a number of other organs are also affected. KALYDECO, an oral medicine known as a CFTR potentiator, helps the CFTR protein function more normally once it reaches the cell surface. KALYDECO targets the abnormal CFTR protein channels and opens them to allow chloride ions to move into and out of the cell, which helps thin the mucus so it can hydrate and protect the airways.

Today's CHMP opinion is based on previously announced data from the first part of a Phase 3, two-part, randomised, double-blind, placebo-controlled, cross-over study of 39 people with CF ages 6 and older who have a non-G551D gating mutation. The first part of the study showed statistically significant improvements in lung function (FEV_1), sweat chloride, BMI and CFQ-R scores. Data from the second part of the study were presented at the European Cystic Fibrosis Society Conference in June 2014 and showed that these improvements were maintained through 24 weeks of treatment with ivacaftor. The safety profile was similar to prior Phase 3 studies of ivacaftor in people with the G551D mutation.

The CHMP's positive opinion will now be reviewed by the European Commission, which has the authority to approve medicines for the European Union. The European Commission generally follows the recommendation of the CHMP and typically issues marketing approval within three to four months.

The CHMP also issued a positive opinion recommending the inclusion of data from the long-term follow-up PERSIST study in the KALYDECO label. PERSIST is a Phase 3, open-label, 96-week, rollover extension trial that evaluated the long-term safety and durability of treatment with KALYDECO by enrolling people ages 6 and older with at least one copy of the G551D mutation who completed 48 weeks of treatment in the Phase 3 ENVISION and STRIVE studies (placebo and KALYDECO treatment groups) and met other eligibility criteria. Results from PERSIST demonstrated that the safety and efficacy of KALYDECO seen in the Phase 3 STRIVE and ENVISION trials was maintained through nearly three years (144 weeks) in G551D patients.

About KALYDECO™ (ivacaftor)

KALYDECO (ivacaftor) is the first medicine to treat the underlying cause of CF in people with specific mutations in the *CFTR* gene. Known as a CFTR potentiator, KALYDECO is an oral medicine that aims to help the CFTR protein function more normally once it reaches the cell surface, to help hydrate and clear mucus from the airways. KALYDECO (150mg, q12h) was first approved by the U.S. Food and Drug Administration in January 2012 for use in people with CF ages 6 and older who have

at least one copy of the G551D mutation and in February 2014 for use in people with CF ages 6 and older who have the following additional *CFTR* mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D. In Canada, KALYDECO was first approved in November 2012 for use in people with CF ages 6 and older who have at least one copy of the G551D mutation and in June 2014 for use in people with CF ages 6 and older who have the following additional *CFTR* mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D and G970R.

KALYDECO was approved by the European Medicines Agency in July 2012, by the Therapeutic Goods Administration in Australia in July 2013, by Medsafe in New Zealand in December 2013 and by Swissmedic in Switzerland in January 2014 for use in people with CF ages 6 and older who have at least one copy of the G551D mutation in the *CFTR* gene.

Vertex retains worldwide rights to develop and commercialize KALYDECO.

INDICATION AND IMPORTANT SAFETY INFORMATION FOR KALYDECO™ (ivacaftor)

Ivacaftor (150 mg tablets) is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the *CFTR* gene.

In the United States, ivacaftor is also indicated for the treatment of CF in patients age 6 and older who have one of the following mutations in the *CFTR* gene: *G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*. In Canada, ivacaftor is indicated for these same mutations and additionally for *G970R*.

Ivacaftor is not effective in patients with CF with 2 copies of the *F508del* mutation (*F508del/F508del*) in the *CFTR* gene. The safety and efficacy of ivacaftor in children with CF younger than 6 years of age have not been established.

Elevated liver enzymes (transaminases; ALT and AST) have been reported in patients receiving ivacaftor. It is recommended that ALT and AST be assessed prior to initiating ivacaftor, every 3 months during the first year of treatment, and annually thereafter. Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal. Following resolution of transaminase elevations, consider the benefits and risks of resuming ivacaftor dosing.

Use of ivacaftor with medicines that are strong CYP3A inducers, such as the antibiotics rifampin and rifabutin; seizure medications (phenobarbital, carbamazepine, or phenytoin); and the herbal supplement St. John's Wort, substantially decreases exposure of ivacaftor and may diminish effectiveness. Therefore, co-administration is not recommended.

The dose of ivacaftor must be adjusted when used concomitantly with strong and moderate CYP3A inhibitors or when used in patients with moderate or severe hepatic disease.

Ivacaftor can cause serious adverse reactions including abdominal pain and high liver enzymes in the blood. The most common side effects associated with ivacaftor include headache; upper respiratory tract infection (the common cold), including sore throat, nasal or sinus congestion, and runny nose; stomach (abdominal) pain; diarrhea; rash; and dizziness. These are not all the possible side effects of ivacaftor. A list of the adverse reactions can be found in the product labeling for each country where ivacaftor is approved. Patients should tell their healthcare providers about any side effect that bothers them or does not go away.

Please see KALYDECO U.S. Prescribing Information, EU Summary of Product Characteristics, Canadian Product Monograph, Australian Consumer Medicine Information and Product Information, Swiss Prescribing Information and Patient Information, and the New Zealand Datasheet and Consumer Medicine Information.

About Cystic Fibrosis

Cystic fibrosis is a rare, life-shortening genetic disease affecting approximately 75,000 people in North America, Europe and Australia. Today, the median predicted age of survival for a person with CF is between 34 and 47 years, but the median age of death remains in the mid-20s.

CF is caused by a defective or missing CFTR protein resulting from mutations in the *CFTR* gene. Children must inherit two defective *CFTR* genes — one from each parent — to have CF. There are more than 1,900 known mutations in the *CFTR* gene. Some of these mutations, which can be determined by a genetic, or genotyping test, lead to CF by creating non-working or too few CFTR protein at the cell surface. The defective function or absence of CFTR proteins in people with CF results in poor flow of salt and water into and out of the cell in a number of organs, including the lungs. This leads to the buildup of abnormally thick, sticky mucus that can cause chronic lung infections and progressive lung damage.

Collaborative History with Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT)

Vertex initiated its CF research program in 1998 as part of a collaboration with CFFT, the nonprofit drug discovery and development affiliate of the Cystic Fibrosis Foundation. This collaboration was expanded to support the accelerated discovery and development of Vertex's CFTR modulators.

About Vertex

Vertex is a global biotechnology company that aims to discover, develop and commercialize innovative medicines so people with serious diseases can lead better lives. In addition to our clinical development programs focused on cystic fibrosis, Vertex has more than a dozen ongoing research programs aimed at other serious and life-threatening diseases.

Founded in 1989 in Cambridge, Mass., Vertex today has research and development sites and commercial offices in the United States, Europe, Canada and Australia. For four years in a row, *Science* magazine has named Vertex one of its Top Employers in the life sciences. For additional information and the latest updates from the company, please visit www.vrtx.com.

Special Note Regarding Forward-looking Statements

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, including, without limitation, statements regarding the European Commission generally following the recommendations of the CHMP and typically issuing marketing approval within three to four months. While Vertex believes the forward-looking statements contained in this press release are accurate, there are a number of factors that could cause actual events or results to differ materially from those indicated by such forward-looking statements. Those risks and uncertainties include, among other things, that Vertex could experience unforeseen delays in obtaining marketing approval from the European Commission and the other risks listed under Risk Factors in Vertex's annual report and quarterly reports filed with the Securities and Exchange Commission and available through the company's website at www.vrtx.com. Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

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