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Vertex Submits Supplemental New Drug Application (sNDA) to U.S. Food and Drug Administration for Use of KALYDECO® (ivacaftor) in People 18 and Older with Cystic Fibrosis who have the R117H Mutation

-Marketing Authorization Application (MAA) variation in Europe planned for third quarter of 2014-

BOSTON--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced the submission of a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) for the approval of KALYDECO® in people with cystic fibrosis (CF) ages 18 and older who have the R117H mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR)* gene. In the United States, KALYDECO is currently approved for use in people with CF ages 6 and older who have one of the following nine mutations: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P or G1349D. CF is caused by a defective or missing CFTR protein that results from mutations in the *CFTR* gene. In the United States, approximately 300 people have the R117H mutation and are 18 years of age or older. R117H is the most common residual function mutation and also has a defect in the gating of the CFTR protein.

"This submission is another step forward in our goal to help more people with this devastating disease," said Jeffrey Chodakewitz, M.D., Senior Vice President and Chief Medical Officer at Vertex. "While people with the R117H mutation exhibit a wide range in the severity of their disease, their lung function often declines as they get older, marking the need for new medicines."

In addition to the sNDA submission, Vertex intends to submit a Marketing Authorization Application (MAA) variation in Europe in the third quarter of 2014 for people with CF ages 18 and older who have the R117H mutation in the *CFTR* gene.

The sNDA submission is based on previously announced data from a Phase 3 study of ivacaftor that enrolled 69 people with CF ages 6 and older who had at least one R117H mutation. The study did not meet its primary endpoint of the mean absolute change from baseline in $ppFEV_1$ (percent predicted forced expiratory volume in one second) for ivacaftor compared to placebo (treatment difference) across all patients, however a pre-specified subset analysis in people who were 18 years of age and older showed statistically significant improvements in lung function ($ppFEV_1$) and other key secondary endpoints.

The subset analysis included 50 people with CF ages 18 and older who had a mean baseline absolute FEV_1 of 65 percent predicted. In these patients, a statistically significant mean absolute treatment difference of 5.0 percentage points (p=0.01) in $ppFEV_1$ was observed through 24 weeks of treatment, which corresponded to a mean relative treatment difference of 9.1 percent (p=0.008). Four weeks following the completion of treatment with ivacaftor, patients in this subset analysis showed a mean absolute within-group decrease of -3.1 percentage points (p=0.001) in $ppFEV_1$. People who took part in this study were eligible to enroll in an open-label rollover study where all patients received ivacaftor after a washout period of at least three weeks. After the first 12 weeks of treatment in the rollover study, the mean absolute improvement from baseline in lung function for patients ages 18 and older (n=46) was 5.1 percentage points ($p < 0.0001$). Across the 24-week study and through 12 weeks of treatment in the rollover study, treatment with ivacaftor also resulted in decreases in sweat chloride and improvements in CFQ-R.

Across all the patients, the safety and tolerability results observed in the 24-week study and rollover study were consistent with those observed in prior Phase 3 studies of ivacaftor in people with CF. In the 24-week study, the most commonly observed adverse events in those who received ivacaftor were infective pulmonary exacerbation, cough and headache, which occurred with similar frequency compared to those who received placebo. Serious adverse events occurred in 17 percent of patients who received placebo versus 12 percent of patients who received ivacaftor. In the rollover study, the most common serious adverse event was infective pulmonary exacerbations.

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 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.

About Cystic Fibrosis

Cystic fibrosis is a rare, life-threatening 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, Dr. Chodakewitz's statements in the second paragraph of this press release and statements regarding Vertex's plan to submit a Marketing Authorization Application (MAA) variation in Europe in the third quarter of 2014. While the company 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 submitting regulatory filings, that regulatory authorities may not approve, or approve on a timely basis, ivacaftor for people with the R117H mutation 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 Vertex's website at www.vrtx.com. Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

(VRTX-GEN)

Vertex Pharmaceuticals Incorporated
Investors:
Michael Partridge, 617-341-6108
or
Kelly Lewis, 617-961-7530
or
Media:
Zach Barber, 617-341-6992
mediainfo@vrtx.com

Source: Vertex Pharmaceuticals Incorporated