FDA Accepts Vertex's Supplemental New Drug Applications for TRIKAFTA® (elexacaftor/tezacaftor /ivacaftor and ivacaftor), SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) and KALYDECO® (ivacaftor) for Additional CFTR Mutations

September 1, 2020

- More than 600 people with certain rare CF mutations could become newly eligible for TRIKAFTA, SYMDEKO or KALYDECO -

BOSTON--(BUSINESS WIRE)--Sep. 1, 2020-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced the U.S. Food and Drug Administration (FDA) accepted three supplemental New Drug Applications (sNDAs) for TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor), SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) and KALYDECO® (ivacaftor). These regulatory submissions are intended to expand the labels for TRIKAFTA, SYMDEKO and KALYDECO to include additional rare *CFTR* mutations, allowing people with cystic fibrosis (CF) not previously eligible for these medicines an opportunity to benefit from treatment that targets the underlying cause of their disease. In addition, these regulatory submissions may also allow certain people with CF who are currently eligible for KALYDECO to become eligible for SYMDEKO or TRIKAFTA and certain people currently eligible for SYMDEKO may become eligible for TRIKAFTA. The FDA has assigned a Prescription Drug User Fee Act (PDUFA) target action date of December 30, 2020. The regulatory submissions are based on data from an *in vitro* cell assay showing that these rare *CFTR* mutations respond to one or more of these CFTR modulator regimens.

"We have spent the last 20 years discovering, developing and bringing new medicines to thousands of people with CF, and the regulatory submissions announced today are an important next step in our commitment to bring transformative medicines to everyone living with this disease," said David Altshuler, M.D., Ph.D., Executive Vice President, Global Research and Chief Scientific Officer. "Using our well-established *in vitro* approach, we have been able to generate data providing evidence that people with certain rare mutations could benefit from treating the underlying cause of their disease with CFTR modulators."

These sNDAs are based on *in vitro* data from a validated cell assay model showing that many rare mutations in the *CFTR* gene are responsive to one or more of Vertex's medicines — KALYDECO, SYMDEKO and TRIKAFTA — beyond the mutations that are currently indicated for these therapies. Approximately 600 people in the U.S. who have certain rare CF mutations may benefit from TRIKAFTA, SYMDEKO or KALYDECO for the first time. In addition, more than 1,100 people with CF in the U.S. currently eligible for SYMDEKO or KALYDECO may have the option of an additional CFTR modulator. These regulatory submissions may allow certain people with CF who are currently eligible for KALYDECO to become eligible for SYMDEKO or TRIKAFTA and certain people currently eligible for SYMDEKO may become eligible for TRIKAFTA.

Data generated from this model, along with Phase 3 clinical data, have already led to the inclusion of nearly 30 additional ultra-rare and rare mutations in the U.S. for KALYDECO and SYMDEKO, including the first ever FDA approval based on *in vitro* data for a KALYDECO label expansion in patients with residual function *CFTR* mutations.

About Cystic Fibrosis

Cystic Fibrosis (CF) is a rare, life-shortening genetic disease affecting approximately 75,000 people worldwide. CF is a progressive, multi-system disease that affects the lungs, liver, GI tract, sinuses, sweat glands, pancreas and reproductive tract. CF is caused by a defective and/or missing CFTR protein resulting from certain mutations in the *CFTR* gene. Children must inherit two defective *CFTR* genes — one from each parent — to have CF. While there are many different types of *CFTR* mutations that can cause the disease, the vast majority of all people with CF have at least one *F508del* mutation. These mutations, which can be determined by a genetic test, or genotyping test, lead to CF by creating non-working and/or too few CFTR proteins at the cell surface. The defective function and/or absence of CFTR protein results in poor flow of salt and water into and out of the cells in a number of organs. In the lungs, this leads to the buildup of abnormally thick, sticky mucus that can cause chronic lung infections and progressive lung damage in many patients that eventually leads to death. The median age of death is in the early 30s.

INDICATION AND IMPORTANT SAFETY INFORMATION FOR KALYDECO® (ivacaftor), SYMDEKO® (tezacaftor/ivacaftor and ivacaftor), and TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor)

What is KALYDECO?

KALYDECO is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 6 months and older who have at least one mutation in their CF gene that is responsive to KALYDECO. Patients should talk to their doctor to learn if they have an indicated CF gene mutation. It is not known if KALYDECO is safe and effective in children under 6 months of age.

What is SYMDEKO?

SYMDEKO is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have two copies of the *F508del* mutation, or who have at least one mutation in the CF gene that is responsive to treatment with SYMDEKO. Patients should talk to their doctor to learn if they have an indicated CF gene mutation. It is not known if SYMDEKO is safe and effective in children under 6 years of age.

What is TRIKAFTA?

TRIKAFTA is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one copy of the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Patients should talk to their doctor to learn if they have an indicated CF gene mutation. It is not known if TRIKAFTA is safe and effective in children under 12 years of age.

Patients should not take KALYDECO, SYMDEKO, or TRIKAFTA if they take certain medicines or herbal supplements, such as: the antibiotics rifampin or rifabutin; seizure medications such as phenobarbital, carbamazepine, or phenytoin; or St. John's wort.

Before taking KALYDECO, SYMDEKO, or TRIKAFTA, patients should tell their doctor about all of their medical conditions, including if they: have kidney problems; have or have had liver problems; are pregnant or plan to become pregnant because it is not known if KALYDECO, SYMDEKO, or TRIKAFTA will harm an unborn baby; or are breastfeeding or planning to breastfeed because it is not known if KALYDECO, SYMDEKO, or TRIKAFTA passes into breast milk. Before taking KALYDECO, patients should tell their doctor if they drink grapefruit juice or eat grapefruit or Seville oranges.

KALYDECO, SYMDEKO, or TRIKAFTA may affect the way other medicines work, and other medicines may affect how KALYDECO, SYMDEKO, or TRIKAFTA work. Therefore, the dose of KALYDECO, SYMDEKO, or TRIKAFTA may need to be adjusted when taken with certain medications. Patients should especially tell their doctor if they take antifungal medications such as ketoconazole, itraconazole, posaconazole, voriconazole, or fluconazole; or antibiotics such as telithromycin, clarithromycin, or erythromycin.

KALYDECO, SYMDEKO, or TRIKAFTA can cause dizziness in some people who take it. Patients should not drive a car, use machinery, or do anything that needs them to be alert until they know how KALYDECO, SYMDEKO, or TRIKAFTA affects them.

Patients should avoid food or drink containing grapefruit or Seville oranges while taking KALYDECO. **Patients should avoid** food or drink containing grapefruit while taking SYMDEKO or TRIKAFTA.

KALYDECO, SYMDEKO, and TRIKAFTA can cause serious side effects, such as:

High liver enzymes in the blood have been reported in patients receiving KALYDECO, SYMDEKO, or TRIKAFTA. The patient's doctor will do blood tests to check their liver before starting treatment with KALYDECO, SYMDEKO, or TRIKAFTA, every 3 months during the first year of treatment, and every year while on treatment. For patients who have had high liver enzymes in the past, the doctor may do blood tests to check the liver more often. Patients should call their doctor right away if they have any of the following symptoms of liver problems: pain or discomfort in the upper right stomach (abdominal) area; yellowing of their skin or the white part of their eyes; loss of appetite; nausea or vomiting; or dark, amber-colored urine.

Abnormality of the eye lens (cataract) in some children and adolescents treated with KALYDECO, SYMDEKO, or TRIKAFTA. If the patient is a child or adolescent, their doctor should perform eye examinations before and during treatment with KALYDECO, SYMDEKO, or TRIKAFTA to look for cataracts.

The most common side effects of KALYDECO include headache; upper respiratory tract infection (common cold), which includes sore throat, nasal or sinus congestion, and runny nose; stomach (abdominal) pain; diarrhea; rash; nausea; and dizziness.

The most common side effects of SYMDEKO include headache, nausea, sinus congestion, and dizziness.

The most common side effects of TRIKAFTA include headache, diarrhea, upper respiratory tract infection (common cold) including stuffy and runny nose, stomach (abdominal) pain, inflamed sinuses, increase in liver enzymes, increase in a certain blood enzyme called creatine phosphokinase, rash, flu (influenza), and increase in blood bilirubin.

These are not all the possible side effects of KALYDECO, SYMDEKO, or TRIKAFTA. **Please click the product link to see the full Prescribing Information for KALYDECO, SYMDEKO, or TRIKAFTA.**

About Vertex

Vertex is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious diseases. The company has multiple approved medicines that treat the underlying cause of cystic fibrosis (CF) — a rare, life-threatening genetic disease — and has several ongoing clinical and research programs in CF. Beyond CF, Vertex has a robust pipeline of investigational small molecule medicines in other serious diseases where it has deep insight into causal human biology, including pain, alpha-1 antitrypsin deficiency and APOL1-mediated kidney diseases. In addition, Vertex has a rapidly expanding pipeline of genetic and cell therapies for diseases such as sickle cell disease, beta thalassemia, Duchenne muscular dystrophy and type 1 diabetes mellitus.

Founded in 1989 in Cambridge, Mass., Vertex's global headquarters is now located in Boston's Innovation District and its international headquarters is in London, UK. Additionally, the company has research and development sites and commercial offices in North America, Europe, Australia and Latin America. Vertex is consistently recognized as one of the industry's top places to work, including 10 consecutive years on Science magazine's Top Employers list and top five on the 2019 Best Employers for Diversity list by Forbes. For company updates and to learn more about Vertex's history of innovation, visit www.vrtx.com or follow us on Facebook, Twitter, LinkedIn, YouTube and Instagram.

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 made by Dr. Altshuler in this press release and statements regarding our expectations relating to the potential approval of TRIKAFTA, SYMDEKO, and KALYDECO for additional *CFTR* mutations, the FDA's target action date and information regarding the review process in the United States, the data supporting product approval, and the number of additional patients that may benefit from our medicines. While Vertex believes the forward-looking statements contained in this press release are accurate, these forward-looking statements represent the company's beliefs only as of the date of this press release and 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 regulatory authorities may not approve, or approve on a timely basis, the three sNDAs, that data from the company's submissions may not support registration or further development of its compounds due to safety, efficacy or other reasons, and 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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