Health Canada Approves PrSYMDEKO™ (tezacaftor/ivacaftor and ivacaftor) to Treat the Underlying Cause of Cystic Fibrosis in People Ages 12 and Older with Certain Mutations in the CFTR Gene

June 28, 2018

-SYMDEKO is Vertex's third medicine to treat the underlying cause of CF-

-Approximately 2,000 people in Canada are ages 12 and older and have two copies of the F508del mutation or at least one mutation in the CF gene that is responsive to treatment with SYMDEKO-

BOSTON--(BUSINESS WIRE)--Jun. 28, 2018-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced that Health Canada approved PrSYMDEKO™ (tezacaftor/ivacaftor and ivacaftor) for treating the underlying cause of cystic fibrosis (CF) in people ages 12 and older who have two copies of the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, or who have one copy of the *F508del* mutation and one of the following mutations in the *CFTR* gene: *P67L*, *D110H*, *R117C*, *L206W*, *R352Q*, *A455E*, *D579G*, *711+3A→G*, *S945L*, *S977F*, *R1070W*, *D1152H*, *2789+5G→A*, *3272-26A→G*, and *3849+10kbC→T*.

"This approval is an important milestone in our journey to enhance and expand treatment options for people living with CF," said Reshma Kewalramani, M.D., Executive Vice President and Chief Medical Officer at Vertex. "We have made rapid progress in developing multiple new medicines over the last year, and will continue to relentlessly invest in our science to treat the underlying cause of CF."

Approval was based on data from two Phase 3 studies (EVOLVE and EXPAND), published in the *New England Journal of Medicine* in November 2017, that enrolled 744 people with CF ages 12 and older with two copies of the *F508del* mutation (n=504) or with one *F508del* mutation and a second mutation predicted to be responsive to tezacaftor/ivacaftor (n=244). Across both studies, patients treated with SYMDEKO experienced statistically significant improvements in lung function, as determined by absolute change from baseline in percent predicted forced expiratory volume in one second ($ppFEV_1$). The treatment was generally well tolerated; the most common adverse reactions (≥10%) experienced by patients who received SYMDEKO in the pooled, placebo-controlled Phase 3 studies were headache (14%) and nasopharyngitis (12%). Results from an interim analysis of the ongoing, 96-week EXTEND Phase 3 rollover study presented at the European Cystic Fibrosis Society (ECFS) Conference earlier this month add to the growing body of evidence supporting the benefit of long-term treatment of the underlying cause of the disease. The analysis demonstrated a safety profile consistent with that observed in the EVOLVE and EXPAND studies and that initial improvements in lung function (measured by absolute change in $ppFEV_1$) observed in the EVOLVE study were sustained for up to 48 weeks.

"Ever since the discovery of the CF gene in Canada, the CF community has been hoping for a therapy that targets the root of the disease," said Elizabeth Tullis, M.D., FRCPC, Director of the Toronto Adult Cystic Fibrosis Clinic at St. Michael's Hospital. "The approval of SYMDEKO brings great hope to people with CF and their families, and provides a new therapy for almost 50 percent of Canadians living with CF."

SYMDEKO was approved by the U.S. Food and Drug Administration (FDA) in February of this year for use in patients aged 12 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. The European Medicines Agency (EMA) has validated the Marketing Authorization Application (MAA) for the tezacaftor/ivacaftor combination. The company expects approval in the EU in the second half of 2018.

About Cystic Fibrosis

Cystic fibrosis is a rare, life-threatening genetic disease affecting approximately 75,000 people in North America, Europe and Australia.

CF is caused by a defective or missing cystic fibrosis transmembrane conductance regulator (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 approximately 2,000 known mutations in the *CFTR* gene. Some of these mutations, which can be determined by a genetic test, or genotyping test, lead to CF by creating non-working or too few CFTR proteins at the cell surface. The defective function or absence of CFTR protein results in poor flow of salt and water into and out of the cell 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 mid-to-late 20s.

About SYMDEKO™ (tezacaftor/ivacaftor and ivacaftor)

Some mutations result in CFTR protein that is not processed or folded normally within the cell, and that generally does not reach the cell surface. SYMDEKO is a combination of tezacaftor and ivacaftor. Tezacaftor is designed to address the trafficking and processing defect of the CFTR protein to enable it to reach the cell surface where ivacaftor can increase the amount of time the protein stays open.

Please click here to see the full U.S. Prescribing Information for SYMDEKO.

U.S. INDICATION AND IMPORTANT SAFETY INFORMATION FOR SYMDEKO™ (tezacaftor/ivacaftor and ivacaftor) tablets

SYMDEKO is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients aged 12 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 12 years of age.

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

Before taking SYMDEKO, patients should tell their doctor if they: have or have had liver problems; have kidney problems; are pregnant or plan to become pregnant because it is not known if SYMDEKO will harm an unborn baby; are breastfeeding or planning to breastfeed because it is not known if SYMDEKO passes into breast milk.

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

SYMDEKO may cause dizziness in some people who take it. Patients should not drive a car, use machinery, or do anything that requires alertness until they know how SYMDEKO affects them.

Patients should avoid food or drink that contains grapefruit or Seville oranges while they are taking SYMDEKO.

SYMDEKO can cause serious side effects, including:

High liver enzymes in the blood, which have been reported in people treated with SYMDEKO or treated with ivacaftor alone. The patient's doctor will do blood tests to check their liver before they start SYMDEKO, every 3 months during the first year of taking SYMDEKO, and every year while taking SYMDEKO. 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 the skin or the white part of the eyes; loss of appetite; nausea or vomiting; dark, amber-colored urine.

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

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

These are not all the possible side effects of SYMDEKO.

About Vertex

Vertex is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious and life-threatening diseases. In addition to clinical development programs in CF, Vertex has more than a dozen ongoing research programs focused on the underlying mechanisms of other serious diseases.

Founded in 1989 in Cambridge, Mass., Vertex's headquarters is now located in Boston'sInnovation District. Today, the company has research and development sites and commercial offices in the United States, Europe, Canada and Australia. Vertex is consistently recognized as one of the industry's top places to work, including being named to Science magazine's Top Employers in the life sciences ranking for eight years in a row.

For additional information and the latest updates from the company, please visit www.vrtx.com.

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

Vertex initiated its CF research program in 2000 as part of a collaboration with CFFT, the nonprofit drug discovery and development affiliate of the Cystic Fibrosis Foundation. KALYDECO® (ivacaftor), ORKAMBI® (lumacaftor/ivacaftor), SYMDEKO™ (tezacaftor/ivacaftor and ivacaftor), VX-659 and VX-445 were discovered by Vertex as part of this collaboration.

Special Note Regarding Forward-looking Statements

This press release contains forward-looking statements, as defined in the Private Securities Litigation Reform Act of 1995, as amended, including the statements by Dr. Kewalramani in the second paragraph and Dr. Tullis in the fourth paragraph of this press release and statements regarding the anticipated timing of approval by the EMA. 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, risks related to obtaining approval and commercializing tezacaftor/ivacaftor in Europe, developing additional medicines to treat cystic fibrosis 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.

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