Vertex Receives Approval for SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) in Australia, to Treat the Underlying Cause of Cystic Fibrosis in People aged 12 and Older with Certain CFTR Gene Mutations

March 12, 2019

-A new treatment option for patients with two copies of the F508del mutation, the most common mutation in cystic fibrosis-

-First medicine in Australia to treat the underlying cause of cystic fibrosis in patients who have certain mutations that result in residual CFTR function-

BOSTON--(BUSINESS WIRE)--Mar. 12, 2019-- Vertex Pharmaceuticals Incorporated today announced that the Therapeutic Goods Administration (TGA) of Australia has granted registration to SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) for the treatment of people with cystic fibrosis (CF) aged 12 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence. Mutations in the *CFTR* gene that produce CFTR protein responsive to SYMDEKO® include *F508del* and mutations in which the CFTR protein shows residual function: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, 3849+10kbC→T, E56K, R74W, D110E, D110H, E193K, E831X, F1052V, K1060T, A1067T, F1074L and D1270N*. SYMDEKO® will be considered for Australian reimbursement for eligible CF patients aged 12 years and older at the March meeting of the Pharmaceutical Benefits Advisory Committee.

"We are delighted that the Therapeutic Goods Administration in Australia recognized the safety profile and efficacy of SYMDEKO®. This approval brings us one step closer to our future goal of bringing treatment to all people living with CF," said Reshma Kewalramani, M.D., Executive Vice President and Chief Medical Officer at Vertex. "This new medicine is an especially important treatment option for patients with residual function mutations and those with two copies of the *F508del* mutation who either never started or discontinued ORKAMBI® (lumacaftor/ivacaftor)."

The TGA's decision is based on results from two pivotal Phase 3 studies, EVOLVE and EXPAND, published in the *New England Journal of Medicine* in November 2017. Results showed treatment with tezacaftor/ivacaftor in combination with ivacaftor provides benefits across different CF populations, including statistically significant improvements in lung function, as determined by absolute change from baseline in percent predicted forced expiratory volume in one second ($ppFEV_1$), with a generally well tolerated safety profile and a lack of increased respiratory adverse events compared to placebo. The improvements in lung function showed a mean absolute change in $ppFEV_1$ compared to placebo of 4.0 percentage points ($P<0.0001$) and 6.8 percentage points ($P<0.0001$) in EVOLVE and EXPAND respectively. The most common adverse reactions (≥10% incidence) experienced by patients who received tezacaftor/ivacaftor in combination with ivacaftor in pooled, placebo-controlled Phase 3 studies were headache and nasopharyngitis.

Tezacaftor/ivacaftor in combination with ivacaftor was approved by the U.S. Food and Drug Administration (FDA) in February 2018, by Health Canada in June 2018 and by the European Commission in October 2018.

About Cystic Fibrosis

Cystic Fibrosis (CF) is a rare, life-shortening 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.

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. **Please click here to see the fullU.S.Prescribing Information for SYMDEKO (tezacaftor/ivacaftor and ivacaftor) tablets.**

About EVOLVE and EXPAND

Data from the two Phase 3 studies EVOLVE and EXPAND were published in the *New England Journal of Medicine* in November 2017. The studies enrolled approximately 750 people with CF ages 12 and older with two copies of the *F508del* mutation or with one *F508del* mutation and a second mutation associated with residual CFTR activity. Across both studies, patients treated with tezacaftor/ivacaftor in combination with ivacaftor experienced statistically significant improvements in lung function, as determined by absolute change from baseline in ppFEV$_1$. The treatment was generally well tolerated. The most common adverse reactions (≥10%) experienced by patients who received tezacaftor/ivacaftor with ivacaftor in the pooled, placebo-controlled Phase 3 studies were headache (14% versus 12% on placebo) and nasopharyngitis (12% versus 10% on placebo).

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, Australia and Latin America. 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 nine years in a row. 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, the expected March meeting of the Pharmaceuticals Benefits Advisory Committee and the quote by Dr. Kewalramani in the second paragraph. 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 data from the company's development programs 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.

(VRTX-GEN)

View source version on businesswire.com: https://www.businesswire.com/news/home/20190312005370/en/

Source: Vertex Pharmaceuticals Incorporated

Vertex Pharmaceuticals Incorporated
Investors:
Michael Partridge, +1-617-341-6108
or
Eric Rojas, +1-617-961-7205
or
Zach Barber, +1-617-341-6470
or
Media:
mediainfo@vrtx.com
or
North America: + 1-617-341-6992
or

Europe & Australia: + 44 20 3204 5275