Vertex Announces European Authorization for Third Cystic Fibrosis Medicine SYMKEVI® (tezacaftor/ivacaftor), to be used in combination with ivacaftor (KALYDECO®), for People with CF Aged 12 and Older with Certain Mutations in the CFTR gene

November 1, 2018

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

- First medicine in the EU to treat the CFTR protein defect in patients who have one copy of the F508del mutation and one copy of one of 14 mutations that result in residual CFTR activity -

LONDON--(BUSINESS WIRE)--Nov. 1, 2018-- Vertex Pharmaceuticals (Europe) Limited, today announced that the European Commission has granted Marketing Authorization for SYMKEVI® (tezacaftor/ivacaftor) in a combination regimen with ivacaftor (KALYDECO®) for the treatment of people with cystic fibrosis (CF) aged 12 and older who either have two copies of the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, or one copy of the *F508del* mutation and a copy of one of the following 14 mutations in which the CFTR protein shows residual activity: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G,* and *3849+10kbC→T*. In addition, the European Medicines Agency's Committee for Orphan Medicinal Products recently recommended the maintenance of orphan designation for tezacaftor/ivacaftor in combination with ivacaftor.

"The authorization of tezacaftor/ivacaftor in combination with ivacaftor is welcome news for European CF patients, their families and everyone involved in their treatment and care. This new medicine is especially important for patients with residual function mutations and those who do not tolerate ORKAMBI® (lumacaftor/ivacaftor)," said Harry Heijerman, Professor and Head of Department of Pulmonology at University Medical Centre Utrecht, The Netherlands.

The EU Marketing Authorization was 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 experienced by patients who received tezacaftor/ivacaftor in combination with ivacaftor in pooled, placebo-controlled Phase 3 studies were headache and nasopharyngitis.

"Today marks an important milestone for many CF patients in Europe, including those who so far have had no available option to treat the CFTR protein defect responsible for their disease," said Reshma Kewalramani, MD, Executive Vice President, Global Medicines Development and Medical Affairs and Chief Medical Officer at Vertex. "With today's Marketing Authorization, we are rapidly moving towards treating 90 percent of CF patients."

Tezacaftor/ivacaftor in combination with ivacaftor was approved by the U.S. Food and Drug Administration (FDA) in February 2018 and by Health Canada in June 2018. It is marketed as SYMDEKO™ in the U.S. and Canada.

About CF
Cystic fibrosis 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 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 build-up 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 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. 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.

For complete product information, please see the Summary of Product Characteristics that can be found on www.ema.europa.eu once posted.

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 orphan designation for medicines

Orphan designation is granted by the European Medicines Agency’s Committee for Orphan Medicinal Products to treatments which either address an existing unmet need or can provide significant benefit for people with life-threatening or chronically debilitating diseases, affecting a small number of patients.

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 eight years in a row.

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 quotes in the second and fourth paragraphs of this press release. 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 commercializing SYMKEVI in Europe and the other risks listed under Risk Factors in Vertex's annual report and quarterly reports filed with the Securities and Exchange Commission. Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

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