Vertex Receives European CHMP Positive Opinion for SYMKEVI® (tezacaftor/ivacaftor) for People with Cystic Fibrosis Aged 12 and Older with Certain Mutations in the CFTR Gene

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If approved, SYMKEVI® (tezacaftor/ivacaftor)will be Vertex's third medicine to treat the CFTR protein defect in patients with cystic fibrosis – a rare life-shortening disease

LONDON--(BUSINESS WIRE)--Jul. 27, 2018-- Vertex Pharmaceuticals (Europe) Limited, today announced that the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion 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*.

If granted Marketing Authorization by the European Commission (EC), tezacaftor/ivacaftorwill be used in combination with ivacaftor and will be the first medicine to treat the CFTR protein defect in CF patients who have one copy of the *F508del* mutation and a copy of one of 14 mutations that result in residual CTFR activity. It also provides a new treatment option for a significant number of people living with CF who have two copies of the *F508del* mutation.

"Our goal at Vertex is to find a cure for all people living with CF and we are moving rapidly towards treating up to 90 percent of patients," said Reshma Kewalramani, MD, Executive Vice President, Global Medicines Development and Medical Affairs and Chief Medical Officer at Vertex. "Today's announcement is a pivotal accomplishment along that journey. If approved, tezacaftor/ivacaftor in combination with ivacaftor represents an important option for people with two copies of the *F508del* mutation and the first medicine in the EU for patients with one copy of the *F508del* mutation and a copy of one of 14 mutations that result in residual CTFR activity."

The regulatory submission was supported by 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 $ppFEV_1$, and with a generally well tolerated safety profile and a lack of increased respiratory adverse events compared to placebo. 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.

"Tezacaftor/ivacaftor combination therapy for CF is another important achievement in the development of disease modulating therapies. This combination improves important clinical outcomes and may benefit those who cannot use ORKAMBI® (lumacaftor/ivacaftor)," said Professor Stuart Elborn, Clinical Professor of Respiratory Medicine, and Centre Director for Specialist Adult Cystic Fibrosis at the Royal Brompton Hospital, London.

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.

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 second mutation that is responsive to tezacaftor/ivacaftor. 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 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 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 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.

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