# FDA Approves ORKAMBI® (lumacaftor/ivacaftor) as First Medicine to Treat the Underlying Cause of Cystic Fibrosis for Children Ages 2-5 Years with Most Common Form of the Disease

August 7, 2018

*- Approximately 1,300 people in the U.S. ages 2 through 5 years have two copies of the F508del mutation, the most common genetic form of the disease -*

BOSTON--(BUSINESS WIRE)--Aug. 7, 2018-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced the U.S. Food and Drug Administration (FDA) has approved ORKAMBI® (lumacaftor/ivacaftor) to include use in children ages 2 through 5 years with cystic fibrosis (CF) who have two copies of the *F508del-CFTR* mutation, making it the first medicine approved to treat the underlying cause of CF in this population. ORKAMBI oral granules are available in two dosage strengths (lumacaftor 100mg/ivacaftor 125mg and lumacaftor 150mg/ivacaftor 188mg) for weight-based dosing. ORKAMBI oral granules should be available for fulfillment within 2 to 4 weeks.

"For the first time, children ages 2 through 5 who have the most common form of CF have a treatment for the underlying cause of their disease," said Reshma Kewalramani, M.D., Executive Vice President and Chief Medical Officer at Vertex. "We believe it is important to treat the underlying cause of the disease as early as possible and this approval is another significant milestone in our journey to bring effective medicines to all people living with CF."

This FDA approval is based on a Phase 3 open-label safety study in 60 patients that showed treatment with ORKAMBI was generally safe and well tolerated for 24 weeks, with a safety profile similar to that in patients ages 6 years and older. Improvements in sweat chloride, a secondary endpoint, were observed at week 24 (mean decrease in sweat chloride from baseline of 31.7 mmol/L; 95% CI: -35.7, -27.6, n=49). Researchers also saw changes in key growth parameters, which were also secondary endpoints in the study. The most common adverse event (≥30%) was cough (63%); most adverse events were mild or moderate in severity. Four patients experienced serious adverse events (2 pulmonary exacerbations, 1 gastroenteritis, 1 constipation) and three patients discontinued treatment due to treatment emergent adverse events or elevated liver function tests. These findings were presented at the 41$^{st}$European Cystic Fibrosis Society Conference in June 2018.

"Cystic fibrosis is a systemic, multi-organ, progressive disease that is present from birth," said Dr. John McNamara, Medical Director of the cystic fibrosis program at Children's Minnesota hospital and lead study researcher. "Research suggests ORKAMBI could impact CF outcomes in patients as young as two years old. This approval is a significant development that enables physicians to begin treating the underlying cause of the disease in this population earlier than ever before."

ORKAMBI was already approved in the U.S. for the treatment of CF in patients ages 6 and older who have two copies of the *F508del-CFTR* mutation. A Marketing Authorization Application (MAA) line extension for ORKAMBI in children ages 2 through 5 years has been submitted to the European Medicines Agency (EMA) with a decision anticipated in the first half of 2019.

**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 ORKAMBI (lumacaftor/ivacaftor)**

ORKAMBI is a combination of lumacaftor, which is designed to increase the amount of mature protein at the cell surface by targeting the processing and trafficking defect of the *F508del* CFTR protein, and ivacaftor, which is designed to enhance the function of the CFTR protein once it reaches the cell surface.

**INDICATION AND IMPORTANT SAFETY INFORMATION FOR ORKAMBI® (lumacaftor/ivacaftor)**
ORKAMBI is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 2 years and older who have two copies of the *F508del* mutation (*F508del/F508del*) in their *CFTR* gene. ORKAMBI should only be used in these patients. It is not known if ORKAMBI is safe and effective in children under 2 years of age.

**Patients should not take ORKAMBI if they are taking certain medicines or herbal supplements, such as:** the antibiotics rifampin or rifabutin; the seizure medicines phenobarbital, carbamazepine, or phenytoin; the sedatives and anti-anxiety medicines triazolam or midazolam; the immunosuppressant medicines cyclosporine, everolimus, sirolimus, or tacrolimus; or St. John's wort.

**Before taking ORKAMBI, patients should tell their doctor about all their medical conditions, including if they:** have or have had liver problems; have kidney problems; have had an organ transplant; or are using birth control. Hormonal contraceptives, including oral, injectable, transdermal, or implantable forms should not be used as a method of birth control when taking ORKAMBI. Patients should tell their doctor if they are pregnant or plan to become pregnant (it is unknown if ORKAMBI will harm the unborn baby) or if they are breastfeeding or planning to breastfeed (it is unknown if ORKAMBI passes into breast milk).

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

**When taking ORKAMBI, patients should tell their doctor if they stop ORKAMBI for more than 1 week** as the doctor may need to change the dose of ORKAMBI or other medicines the patient is taking.

**ORKAMBI can cause serious side effects, including:**

**Worsening of liver function** in people with severe liver disease. The worsening of liver function can be serious or cause death. Patients should talk to their doctor if they have been told they have liver disease as their doctor may need to adjust the dose of ORKAMBI.

**High liver enzymes in the blood,** which can be a sign of liver injury**.** The patient's doctor will do blood tests to check their liver before they start ORKAMBI, every three months during the first year of taking ORKAMBI, and annually thereafter. The patient should call the 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; or confusion.

**Breathing problems** such as shortness of breath or chest tightness in patients when starting ORKAMBI, especially in patients who have poor lung function. If a patient has poor lung function, their doctor may monitor them more closely when starting ORKAMBI.

**An increase in blood pressure** in some people receiving ORKAMBI. The patient's doctor should monitor their blood pressure during treatment with ORKAMBI.

**Abnormality of the eye lens (cataract)** in some children and adolescents receiving ORKAMBI. For children and adolescents, the patient's doctor should perform eye examinations before and during treatment with ORKAMBI to look for cataracts.

**The most common side effects of ORKAMBI include:** breathing problems, such as shortness of breath and chest tightness; nausea; diarrhea; fatigue; increase in a certain blood enzyme called creatinine phosphokinase; rash; gas; common cold, including sore throat, stuffy or runny nose; flu or flu-like symptoms; and irregular, missed, or abnormal periods (menses) and increase in the amount of menstrual bleeding.

**Side effects seen in children** are similar to those seen in adults and adolescents. Additional common side effects seen in children include: cough with sputum, stuffy nose, headache, stomach pain, and increase in sputum.

**Please click here to see the full Prescribing Information for ORKAMBI.**

**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. McNamara in the fourth paragraph of this press release and statements regarding (i) the timing of shipping of the oral granules in the United States and (ii) the anticipated timing of an EMA decision on the MAA line extension. 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, that regulatory authorities may not approve, or approve on a timely basis, the company's drug candidates due to safety, efficacy or other reasons, 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.

(VRTX-GEN)

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