Trikafta™ (elexacaftor/tezacaftor/ivacaftor; ivacaftor) – New orphan drug approval

- On October 21, 2019, the FDA announced the approval of Vertex's Trikafta (elexacaftor/tezacaftor/ivacaftor; ivacaftor), for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.

    — If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one *F508del* mutation.

- CF, a rare, progressive, life-threatening disease, results in the formation of thick mucus that builds up in the lungs, digestive tract, and other parts of the body. It leads to severe respiratory and digestive problems as well as other complications such as infections and diabetes. CF is caused by a defective protein that results from mutations in the *CFTR* gene. While there are approximately 2,000 known mutations of the *CFTR* gene, the most common mutation is the *F508del* mutation.

- Trikafta is a combination of three drugs that target the defective CFTR protein. It helps the protein made by the *CFTR* gene mutation function more effectively. Currently available therapies that target the defective protein are treatment options for some patients with CF, but many patients have mutations that are ineligible for treatment.

    — Trikafta is the first approved treatment that is effective for CF patients 12 years and older with at least one *F508del* mutation, which affects 90% of the population with CF or roughly 27,000 people in the U.S.

- The efficacy of Trikafta was established in two randomized, double-blind studies in patients with CF aged 12 years and older. Study 1 was a 24-week, placebo-controlled study in 403 patients who had an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor. Study 2 was a 4-week, active-controlled study in 107 patients who were homozygous for the *F508del* mutation. In study 2, patients were randomized to receive Trikafta or Symdeko® (tezacaftor/ivacaftor; ivacaftor). The primary efficacy endpoint was the mean absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$).

    — In study 1, the treatment difference between Trikafta and placebo for the mean absolute change from baseline in $ppFEV_1$ at week 4 was 13.8 percentage points (95% CI: 12.1, 15.4; $p < 0.0001$). The treatment difference was sustained through week 24. The number of pulmonary exacerbation events (event rate per year calculated based on 48 weeks per year) from baseline through week 24 was 0.37 and 0.98 for Trikafta and placebo, respectively ($p < 0.0001$).
    — In study 2, treatment with Trikafta vs. Symdeko resulted in a statistically significant improvement in $ppFEV_1$ of 10.0 percentage points (95% CI: 7.4, 12.6; $p < 0.0001$).

- Warnings and precautions for Trikafta include liver function test elevations, concomitant use with CYP3A inducers, concomitant use with CYP3A inhibitors, and cataracts.

- The most common adverse reactions (≥ 5% and at a frequency higher than placebo by ≥ 1%) with Trikafta use were headache, upper respiratory tract infection, abdominal pain, diarrhea, rash, increased alanine aminotransferase, nasal congestion, increased blood creatine phosphokinase, increased aspartate aminotransferase, rhinorrhea, rhinitis, influenza, sinusitis and increased blood bilirubin.

Continued . . .

- The recommended dose of Trikafta is two tablets (each containing elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg) taken orally in the morning and one ivacaftor tablet (containing ivacaftor 150 mg) taken orally in the evening, approximately 12 hours apart.

    — Trikafta should be taken with fat-containing food. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs, cheeses, nuts, whole milk, or meats.

- Trikafta will be priced at $23,896 per 28-day pack or approximately $311,500 per year.

- Vertex's launch plans for Trikafta are pending. Trikafta will be available as a co-package of fixed-dose combination tablets containing elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg, and ivacaftor 150 mg tablets.