Alyftrek™ (vanzacaftor/tezacaftor/deutivacaftor) – New orphan drug approval

- On December 20, 2024, Vertex announced the FDA approval of Alyftrek (vanzacaftor/tezacaftor/deutivacaftor), for the **treatment of cystic fibrosis (CF) in patients 6 years of age and older who have at least one F508del mutation or another responsive 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 indicated mutation.
- CF is a rare, progressive, multi-organ disease that affects the lungs, liver, pancreas, gastrointestinal tract, sinuses, sweat glands and reproductive tract. CF is caused by a defective and/or missing CFTR protein resulting from certain mutations in the *CFTR* gene.
    - There are many different types of *CFTR* mutations that can cause the disease, but most people with CF have at least one *F508del* mutation. In the lungs, CF leads to abnormally thick, sticky mucus, chronic lung infections and progressive lung damage that eventually leads to death for many patients.
- Alyftrek is Vertex's fifth approved CFTR modulator.
- The efficacy of Alyftrek was established in two randomized, double-blind, active-controlled studies in 971 patients aged 12 years and older with CF who have at least one *F508del* mutation or a responsive mutation in the *CFTR* gene. Patients were randomized to Alyftrek or Trikafta® (elexacaftor/tezacaftor/ivacaftor; ivacaftor). In both studies, the primary endpoint evaluated non-inferiority in mean absolute change in percent predicted Forced Expiratory Volume in 1 second ($ppFEV_1$) from baseline through week 24 and a key secondary endpoint evaluated the mean absolute change from baseline in sweat chloride (SwCl) through week 24.
    - In study 1, treatment with Alyftrek resulted in a least squares (LS) mean difference of 0.2 percentage points (95% CI: -0.7, 1.1) in absolute change in $ppFEV_1$ compared to Trikafta. In study 2, treatment with Alyftrek resulted in an LS mean difference of 0.2 percentage points (95% CI: -0.5, 0.9) in absolute change in $ppFEV_1$ compared to Trikafta. As the lower bounds of the 95% CI of the LS mean difference were greater than -3.0 percentage points (the pre-specified non-inferiority margin), **these results demonstrate non-inferiority of Alyftrek to Trikafta**.
    - **SwCl levels were significantly reduced with Alyftrek compared to Trikafta**. In study 1, the LS mean difference in SwCl (mmol/L) between Alyftrek and Trikafta was -8.4 (95% CI: -10.5, -6.3; $p < 0.0001$). In study 2, the LS mean difference was -2.8 (95% CI: -4.7, -0.9; $p = 0.0034$).
- Alyftrek carries a boxed warning for drug-induced liver injury and liver failure.
- Additional warnings and precautions for Alyftrek include hypersensitivity reactions, including anaphylaxis; patients who discontinued or interrupted elexacaftor, tezacaftor, or ivacaftor-containing drugs due to adverse reactions; reduced effectiveness with concomitant use with CYP3A inducers; adverse reactions with concomitant use with CYP3A inhibitors; and cataracts.
- The most common adverse reactions (≥ 5% and at a frequency higher than Trikafta by ≥ 1%) with Alyftrek use were cough, nasopharyngitis, upper respiratory tract infection, headache, oropharyngeal

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pain, influenza, fatigue, increased alanine aminotransferase, rash, increased aspartate aminotransferase, and sinus congestion.

- The recommended dose of Alyftrek in adult and pediatric patients aged 6 years and older is provided in the table below. **Alyftrek is administered orally with fat-containing food, once daily**, at approximately the same time each day.

Age	Weight	Once daily oral dosage
6 to less than 12 years old	Less than 40 kg	Three tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50 mg (total dose of vanzacaftor 12 mg/tezacaftor 60 mg/ deutivacaftor 150 mg)
	Greater than or equal to 40 kg	Two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg (total dose of vanzacaftor 20 mg/tezacaftor 100 mg/ deutivacaftor 250 mg)
12 years and older	Any weight	Two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deutivacaftor 125 mg (total dose of vanzacaftor 20 mg/tezacaftor 100 mg/ deutivacaftor 250 mg)

- Vertex's launch plans for Alyftrek are pending. Alyftrek will be available as fixed-dose combination tablets containing:
    - Vanzacaftor 4 mg, tezacaftor 20 mg, and deutivacaftor 50 mg
    - Vanzacaftor 10 mg, tezacaftor 50 mg, and deutivacaftor 125 mg.