Vertex Announces US FDA Approval of ALYFTREK™, a Once-Daily Next-in-Class CFTR Modulator for the Treatment of Cystic Fibrosis

December 20, 2024

- ALYFTREK ™ is approved for patients 6 years and older with at least one responsive mutation, including 31 additional mutations not responsive to other CFTR modulator therapies -

- In head-to-head clinical trials, ALYFTREK was non-inferior on ppFEV$_1$ and further decreased sweat chloride compared to TRIKAFTA® -

BOSTON--(BUSINESS WIRE)--Dec. 20, 2024-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced that the U.S. Food and Drug Administration (FDA) has approved ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor), a once-daily next-in-class triple combination cystic fibrosis transmembrane conductance regulator (CFTR) modulator for the treatment of cystic fibrosis (CF) in people 6 years and older who have at least one *F508del* mutation or another mutation in the *CFTR* gene that is responsive to ALYFTREK. See below for Important Safety Information, including a Boxed Warning.

“ALYFTREK is our fifth CFTR modulator to secure FDA approval and represents another significant milestone in our journey to serially innovate and to improve the lives of people living with cystic fibrosis,” said Reshma Kewalramani, M.D., Chief Executive Officer and President of Vertex. “Our north star for more than 20 years has been to address the underlying cause of cystic fibrosis, treat more people with this disease, and bring more people to normal levels of CFTR function — ALYFTREK, with once-daily dosing, efficacy in 31 additional mutations, and lower sweat chloride levels than TRIKAFTA, is another step in achieving this goal.”

This approval is based on the most comprehensive Phase 3 pivotal program ever conducted in CF, including more than 1,000 patients across more than 20 countries and more than 200 sites. These data were previously released at the conclusion of the studies and presented at the North American Cystic Fibrosis Conference in September of this year. The Phase 3 studies in people with CF ages 12 years and older met their primary endpoint (non-inferiority on absolute change from baseline in ppFEV$_1$ compared to TRIKAFTA) and all key secondary endpoints (including absolute change from baseline in sweat chloride [SwCl] compared to TRIKAFTA). In the Phase 3 study of children with CF ages 6-11 years, ALYFTREK demonstrated safety, the primary endpoint. Secondary endpoints, such as absolute change from baseline in ppFEV$_1$ and absolute change from baseline in SwCl, were presented, supporting the benefit of ALYFTREK in this age group. ALYFTREK was generally well tolerated across all studies.

“In Phase 3 clinical trials, across a broad range of genotypes, once-daily ALYFTREK demonstrated non-inferiority to TRIKAFTA in ppFEV $_1$ response and statistically significant improvement in SwCl, a welcomed advancement for the treatment of CF,” said Claire L. Keating, M.D., Co-Director of the Gunnar Esiason Adult Cystic Fibrosis and Lung Program at Columbia University and investigator in the ALYFTREK clinical trial program. “ALYFTREK has the potential to improve the care of patients with CF.”

ALYFTREK is the first, once-daily CFTR modulator. In a recent survey, approximately 75% of physicians reported that more convenient dosing is a very high unmet need for people with CF. Specifically, people with CF will have the added benefit from a once-daily dosing regimen, given the need to take CFTR modulators with fat-containing food. ALYFTREK also offers a potentially transformative option for approximately 150 people with CF in the U.S. with one of 31 mutations who are now eligible for a CFTR modulator for the first time.

ALYFTREK was also submitted to global health authorities and is under regulatory review in the European Union, the United Kingdom, Canada, Switzerland, Australia and New Zealand.

About Cystic Fibrosis

Cystic fibrosis (CF) is a rare, life-shortening genetic disease affecting more than 92,000 people globally. CF is a progressive, multi-organ disease that affects the lungs, liver, pancreas, GI 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. Children must inherit two defective *CFTR* genes — one from each parent — to have CF, and these mutations can be identified by a genetic test. While there are many different types of *CFTR* mutations that can cause the disease, the vast majority of people with CF have at least one *F508del* mutation. *CFTR* mutations lead to CF by causing CFTR protein to be defective or by leading to a shortage or absence of CFTR protein at the cell surface. The defective function and/or absence of CFTR protein results in poor flow of salt and water into and out of the cells in a number of organs. In the lungs, this leads to the buildup of abnormally thick, sticky mucus, chronic lung infections and progressive lung damage that eventually leads to death for many patients. The median age of death is in the 30s, but with treatment, projected survival is improving.

Learn more about the importance of sweat chloride (SwCl) in cystic fibrosis.

Today Vertex CF medicines are treating over 68,000 people with CF across more than 60 countries on six continents. This represents 2/3 of the diagnosed people with CF eligible for CFTR modulator therapy.

ALYFTREK U.S. INDICATIONS

ALYFTREK is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years 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.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: DRUG-INDUCED LIVER INJURY AND LIVER FAILURE

Elevated transaminases have been observed in patients treated with ALYFTREK. Cases of serious and potentially fatal drug-induced liver injury and liver failure were reported in patients taking a fixed-dose combination drug containing elexacaftor, tezacaftor, and ivacaftor, which contains the same or similar active ingredients as ALYFTREK. Liver injury has been reported within the first month of therapy and up to 15 months following initiation of elexacaftor/tezacaftor/ivacaftor.

Assess liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) in all patients prior to initiating ALYFTREK, every month during the first 6 months of treatment, every 3 months for the next 12 months, and at least annually thereafter. Consider more frequent monitoring for patients with a history of liver disease or elevated liver function tests (LFTs) at baseline.

Interrupt ALYFTREK for significant elevations in LFTs or in the event of signs or symptoms of liver injury. Consider referral to a hepatologist. Follow patients closely with clinical and laboratory monitoring until abnormalities resolve. If resolved, resume treatment only if benefit is expected to outweigh risk. Closer monitoring is advised after resuming ALYFTREK.

ALYFTREK should not be used in patients with severe hepatic impairment (Child-Pugh Class C). ALYFTREK is not recommended in patients with moderate hepatic impairment (Child-Pugh Class B) and should only be considered when there is a clear medical need, and benefit outweighs risk. If used, monitor patients closely.

WARNINGS AND PRECAUTIONS

Drug-Induced Liver Injury and Liver Failure

- Elevated transaminases have been observed in patients treated with ALYFTREK. Cases of serious and potentially fatal drug-induced liver injury and liver failure have been reported in patients with and without a history of liver disease taking a fixed-dose combination drug containing elexacaftor, tezacaftor, and ivacaftor (ELX/TEZ/IVA), which contains the same or similar active ingredients as ALYFTREK. Liver injury has been reported within the first month of therapy and up to 15 months following initiation of ELX/TEZ/IVA
- Assess LFTs (ALT, AST, alkaline phosphatase, and bilirubin) in all patients prior to initiating ALYFTREK, every month during the first 6 months of treatment, every 3 months for the next 12 months, and at least annually thereafter. Consider more frequent monitoring in patients with a history of liver disease, elevated LFTs at baseline, or a history of elevated LFTs with drugs containing ELX, TEZ, and/or IVA
- Interrupt ALYFTREK in the event of signs or symptoms of liver injury, which may include:
    - Significant elevations in LFTs (e.g., ALT or AST >5x the upper limit or normal (ULN) or ALT or AST >3x ULN with bilirubin >2x ULN)
    - Clinical signs or symptoms suggestive of liver injury (e.g., jaundice, right upper quadrant pain, nausea, vomiting, altered mental status, ascites)
- Consider referral to a hepatologist and follow patients closely with clinical and laboratory monitoring until abnormalities resolve. If resolved and if benefit is expected to outweigh risk, resume ALYFTREK with close monitoring
- ALYFTREK should not be used in patients with severe hepatic impairment. ALYFTREK is not recommended in patients with moderate hepatic impairment and should only be considered when there is a clear medical need and benefit outweighs risk. If used, monitor patients closely

Hypersensitivity Reactions, Including Anaphylaxis

- Hypersensitivity reactions, including cases of anaphylaxis, have been reported in the postmarketing setting of drugs containing ELX, TEZ, and/or IVA (same or similar active ingredients in ALYFTREK). If signs or symptoms of serious hypersensitivity reactions develop during ALYFTREK treatment, discontinue ALYFTREK and institute appropriate therapy. Consider benefits and risks for the individual patient to determine whether to resume ALYFTREK

Patients Who Discontinued or Interrupted Elexacaftor-, Tezacaftor-, or Ivacaftor-Containing Drugs Due to Adverse Reactions

- There are no available safety data for ALYFTREK in patients who previously discontinued or interrupted treatment with drugs containing ELX/TEZ/IVAr due to adverse reactions. Consider the benefits and risks before using ALYFTREK in these patients. If ALYFTREK is used in these patients, closely monitor for adverse reactions as clinically appropriate

Reduced Effectiveness with Concomitant Use With CYP3A Inducers

- Following concomitant use of strong or moderate CYP3A inducers with ALYFTREK, exposures of vanzacaftor, tezacaftor, and deutivacaftor were decreased, which may reduce ALYFTREK effectiveness. Concomitant use with strong or moderate CYP3A inducers is not recommended

Adverse Reactions with Concomitant Use With CYP3A Inhibitors

- Following concomitant use of strong or moderate CYP3A inhibitors with ALYFTREK, exposures of vanzacaftor, tezacaftor, and deutivacaftor were increased, which may increase the risk of adverse reactions associated with ALYFTREK. Reduce the ALYFTREK dosage with concomitant use of strong or moderate CYP3A inhibitors

Cataracts

- Non-congenital lens opacities have been reported in pediatric patients treated with drugs containing ivacaftor (similar to an active ingredient in ALYFTREK). Baseline and follow-up ophthalmological examinations are recommended in pediatric patients treated with ALYFTREK

ADVERSE REACTIONS

Serious Adverse Reactions

- Serious adverse reactions that occurred more frequently with ALYFTREK than with ELX/TEZ/IVA in 2 or more patients (≥0.4%) were influenza (1.5%), increased AST (0.4%), increased GGT (0.4%), depression (0.4%), and syncope (0.4%)

Most Common Adverse Reactions

- The most common adverse reactions to ALYFTREK (≥5% of patients and at a frequency higher than ELX/TEZ/IVA by ≥1%) were cough, nasopharyngitis, upper respiratory tract infection, headache, oropharyngeal pain, influenza, fatigue, increased ALT, rash, increased AST, and sinus congestion

USE IN SPECIFIC POPULATIONS

Pediatric Use

- The safety and effectiveness of ALYFTREK in patients <6 years of age have not been established

Please click here to see the full U.S. Prescribing Information, including Boxed WARNING for ALYFTREK.

About Vertex

Vertex is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious diseases. The company has approved medicines that treat the underlying causes of multiple chronic, life-shortening genetic diseases — cystic fibrosis, sickle cell disease and transfusion-dependent beta thalassemia — and continues to advance clinical and research programs in these diseases. Vertex also has a robust clinical pipeline of investigational therapies across a range of modalities in other serious diseases where it has deep insight into causal human biology, including acute and neuropathic pain, APOL1-mediated kidney disease, IgA nephropathy, primary membranous nephropathy, autosomal dominant polycystic kidney disease, type 1 diabetes and myotonic dystrophy type 1.

Vertex was founded in 1989 and has its global headquarters in Boston, with international headquarters in London. Additionally, the company has research and development sites and commercial offices in North America, Europe, Australia, Latin America and the Middle East. Vertex is consistently recognized as one of the industry's top places to work, including 15 consecutive years on Science magazine's Top Employers list and one of Fortune's 100 Best Companies to Work For. For company updates and to learn more about Vertex's history of innovation, visit www.vrtx.com or follow us on LinkedIn, Facebook, Instagram, YouTube and X.

Special Note Regarding Forward-Looking Statements

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, including, without limitation, statements made by Reshma Kewalramani, M.D., and Claire L. Keating, M.D., in this press release, statements regarding the eligible patient population for ALYFTREK, expectations for ALYFTREK regulatory submissions to global health authorities, and statements regarding the potential benefits of ALYFTREK, including for patients eligible for a CFTR modulator for the first time. While Vertex believes the forward-looking statements contained in this press release are accurate, these forward-looking statements represent the company's beliefs only as of the date of this press release and 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 risks listed under the heading “Risk Factors” in Vertex's annual report and in subsequent filings filed with the Securities and Exchange Commission and available through the company's website at www.vrtx.com and www.sec.gov. You should not place undue reliance on these statements. Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

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Source: Vertex Pharmaceuticals Incorporated