



© Copyright 2024 Oregon State University. All Rights Reserved

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | Fax 503-947-2596



Drug Class Update with New Drug Evaluation: Oral Cystic Fibrosis Modulators

Date of Review: October 2025

Date of Last Review: June 2021 (Prior Authorization update),
June 2020 (modulators class update)

Generic Name: vanzacaftor/tezacaftor/deutivacaftor

Dates of Literature Search: 01/31/2020 – 09/01/2025

Brand Name (Manufacturer): Alyftrek™ (Vertex)

Dossier Received: Yes

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

The purpose of this class update is to evaluate new evidence for the safety and effectiveness of oral cystic fibrosis (CF) modulators in reducing respiratory symptoms or pulmonary exacerbations associated with CF and improving quality of life, as well as to evaluate the evidence and place in therapy of vanzacaftor/tezacaftor/deutivacaftor (VNZ/TEZ/D-IVA).

Plain Language Summary:

- Cystic Fibrosis (CF) is a chronic (long-term) disease that affects the lungs and other organs. CF medications taken by mouth, called modulators, help fix the protein problem caused by changes in the CF gene.
- The review found that the triple therapy called Trikafta® (elexacaftor/tezacaftor/ivacaftor) helps many patients with the most common CF gene mutation (called F508del) breathe better and improves their quality of life compared to older treatments. A new drug, Alyftrek™ (vanzacaftor/tezacaftor/deutivacaftor), works about as well as Trikafta but has less information available, especially in children and in people who have not used Trikafta before.
- Both medicines can cause side effects, such as stomach upset or liver problems, so regular blood tests are needed.
- Not all CF mutations respond to these medicines, and people with rare gene types may have fewer options. The Oregon Drug Use Research and Management (DURM) program recommends keeping Alyftrek as a non-preferred drug, meaning it will need special approval before it is covered, called prior authorization.

Research Questions:

1. What is the comparative evidence for oral CF modulators in improving clinically important outcomes such as respiratory symptoms, pulmonary exacerbations, mortality and quality of life in children and adults with CF? If comparative evidence remains insufficient, does any new evidence change previous conclusions regarding the effectiveness or efficacy of the CF modulators?

2. What are the comparative harms of oral CF modulators in patients being treated for CF? If comparative evidence remains insufficient, does any new evidence change previous conclusions regarding the safety of the CF modulators?
3. Are there subpopulations of patients with CF based on a specific gene mutation, disease severity, race, age, or sex, for which one of the oral CF modulators are more effective or associated with greater harm than other populations?

Conclusions:

- There is moderate quality evidence that triple therapy with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) is more effective than placebo and dual therapy with TEZ/IVA on the respiratory domain of quality of life and change from baseline in percent predicted forced expiratory volume (ppFEV₁). There is insufficient data and too few deaths in clinical trials to assess oral CF modulators on survival in patients with CF.¹⁻⁴
- Majority of data on efficacy and safety of oral CF modulators includes patients with at least one F508del mutation. There is limited data on more rare variants. This remains a concern as there are racial and ethnic variations in variants causing disparities in access to effective treatments.^{5,6}
- There is moderate quality evidence that VNZ/TEZ/D-IVA is non-inferior to ELX/TEZ/IVA on change from baseline in ppFEV₁ through 24 weeks in patients with stable CF with at least one copy of the F508del variant with previous use of ELX/TEZ/IVA.⁷ The generalizability to patients who are naïve or intolerant to ELX/TEZ/IVA is limited. Most patients in the trials were adults (85%) and more evidence is needed in young children and adolescents.
- There is insufficient evidence evaluating VNA/TEZ/D-IVA on quality of life, survival, and pulmonary exacerbations.
- There are limited data supporting the efficacy and safety of VNZ/TEZ/D-IVA in subjects with non-F508del triple combination responsive (i.e., responsive to ELX/TEZ/IVA based on in vitro data) variants. Approval of these variant was based on limited subjects or in vitro data.⁷
- There is low quality evidence that TEZ/IVA does not lead to clinically meaningful benefits in absolute change from baseline in ppFEV₁ compared to IVA alone in subjects with CF, heterozygous for the F508del mutation and a CFTR gating variant (difference 0.3%; 95% CI -0.8 to 1.4).⁸
- Guidelines from the National Institute for Health and Care Excellence (NICE) recommend routine use of CFTR modulators, including ELX/TEZ/IVA, TEZ/IVA, LUM/IVA and VNZ/TEZ/D-IVA based on evidence of clinical benefit and since symptomatic care for CF can be burdensome and does not treat the underlying cause.^{9,10}

Recommendations:

- Maintain vanzacaftor/tezacaftor/deutivacaftor (Alyftrek) as non-preferred on the preferred drug list (PDL) and include in clinical prior authorization (PA) criteria ensuring use is for FDA approved CFTR mutations and according to FDA labeling.
- After evaluation of comparative costs in executive session, no PDL changes were made.
- Update PA criteria with new indications and dosing and to address appropriate step-therapy based on current guidelines.

Summary of Prior Reviews and Current Policy

- There is insufficient evidence that the oral CF transmembrane conductance regulator (CFTR) modulators (potentiators and correctors), improve survival and overall health-related quality of life (other than the respiratory domain).^{11,12}
- For subjects with CF homozygous for the F508del mutation, there is moderate evidence of no significant difference in quality of life (CFQ-R) for the respiratory domain or lung function between ivacaftor (IVA) and placebo.¹³ There is moderate quality evidence of an improvement in lung function, as measured by the percent predicted forced expiratory volume in one second (ppFEV₁) change from baseline with tezacaftor/ivacaftor (TEZ/IVA) and lumacaftor/ivacaftor (LUM/IVA) compared to placebo.¹¹ There is also moderate quality evidence of a decrease in pulmonary exacerbations for both LUM/IVA hazard ratio (HR) 0.61 (95% CI 0.49 to 0.76) and TEZ/IVA (HR 0.64; 95% CI 0.46 to 0.89) compared to placebo.¹¹

- There is moderate strength evidence that IVA alone provides no respiratory benefit in those with R177H rotation.¹³
- There is moderate quality evidence that elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) improves ppFEV1 from baseline to week 4 compared to placebo in those heterozygous for the F508del mutation and a second minimal function mutation with a least squares (LS) mean treatment difference of 13.8% (95% CI 12.1 to 15.4).¹⁴ There is low quality evidence of a decrease in pulmonary exacerbations through week 24 (rate ratio 0.37; 95% CI 0.25 to 0.55) in this population.¹⁴
- There is low quality evidence that ELX/TEZ/IVA improves respiratory function compared to TEZ/IVA in those homozygous for the F508del mutation with a change from baseline in ppFEV1 at week 4 of 10.4% with ELX/TEZ/IVA and 0.4% with TEZ/IVA (LS mean difference 10%; 95% CI 7.4 to 12.6).¹⁵ There is insufficient evidence that ELX/TEZ/IVA improves pulmonary exacerbations compared to TEZ/IVA in this population.
- There is insufficient clinical data in many of the uncommon CFTR mutations that are included in the FDA approved indication of ELX/TEZ/IVA.
- There is insufficient data on the long-term safety of ELX/TEZ/IVA. There are safety concerns regarding the side effects of elevations in liver transaminases and bilirubin, rhabdomyolysis, elevated creatinine kinase, and rash. More data are needed to assess the long-term safety of ELX/TEZ/IVA.

Background:

Cystic Fibrosis (CF) is an autosomal recessive condition that can affect multiple organs, of which progressive lung disease is responsible for approximately 85% of mortality observed in this population.¹⁶ Historically, treatments for CF focused on symptom management and treatment of chronic infection, including antibiotics, dornase alfa, inhaled hypertonic saline, inhaled corticosteroids, oral nonsteroidal anti-inflammatory drugs, and inhaled bronchodilators.¹⁷ CF is caused by mutations in the CFTR gene. CFTR proteins are found on the surface of cells in a variety of tissues where it functions as a regulator of the chloride ion channel.¹⁸ CFTR mutations are often categorized according to their functional impact on CFTR protein synthesis or function (**Table 1**). Over 2000 mutations have been identified in the CFTR gene, with different protein defects resulting from the mutation.^{19,20} The F508del mutation results in misprocessing of CFTR resulting in failure of CFTR to travel to the cell surface, while the G551D and other gating mutations result in failure of CFTR protein channels to open at the cell surface. Lastly, the R117H mutation affects chloride conductance in the pore region of the channel leading to poor conductance of chloride ions.¹⁹ There are three common alleles at the poly-T locus of the R117H gene (5T, 7T, 9T), with the 5T variant associated with greater severity of CF.²¹ Of the various clinical symptoms of CF, only pancreatic function has been shown to correlate well with CFTR genotype. The most common CFTR mutation is the F508del (Class II mutation), which carries the most severe prognosis.²² In the United States, approximately 90% of CF patients carry at least one allele and 50% are homozygous for the F508del mutation. In contrast, approximately 5% of those with CF exhibit residual CFTR ion transport. These residual function mutations cause disease with a more delayed onset than more common forms.²³ Due to racial and ethnic difference in mutation frequency, there are large disparities in access to effective CFTR modulators.^{5,6} Non-White persons have a higher frequency of more rare variants, and there are racial and ethnic differences in cystic fibrosis variants particularly for people of non-European descent who are more likely to have mutations unresponsive to modulator treatment.²⁰ Approximately 30,000 people in the US have CF.²⁴

Table 1: CFTR mutation categories^{20,25}

Class	Description	Prevalence	Examples
Class I: protein production mutations	No functional CFTR created	22%	Gly542x
Class II: protein processing mutations	CFTR protein created, but misfolded, keeping it from reaching the cell surface	88%	F508del
Class III: gating mutations	CFTR protein created and reaches cell surface, but does not function properly	6%	G551D
Class IV: conduction mutations	Opening in CFTR protein ion channel is faulty	6%	R117H
Class V: insufficient protein mutations	CFTR created in insufficient quantities	< 5%	3849 + 10kbc

Clinically meaningful outcomes of CF treatment include mortality, frequency of pulmonary exacerbations, quality of life and respiratory symptoms. Forced expiratory volume in one second (FEV₁) is a commonly used surrogate outcome in clinical trials. A minimal clinically important difference for FEV₁ has not been defined or agreed upon because of the heterogeneous nature of the condition.²⁶ According to National Institute of Clinical Excellence (NICE), an absolute change in ppFEV₁ of 5% or more would be considered clinically important.²⁶ Changing the FEV₁ rate of decline would be the most meaningful effect, but would require a long study duration. In CF patients, FEV₁ decreases on average by 1-3% per year but varies based on age and baseline lung function.²⁷ In CF patients with moderate to severe lung disease, inhaled tobramycin and dornase alfa have shown improvement in FEV₁ ranging from 7.8%-12% with inhaled tobramycin and 5.8%-7.3% with dornase alfa.²⁸ There is also fair evidence to suggest that macrolide antibiotics provide benefit for all levels of disease with improvements in FEV₁ from 3.6%-6.2%.²⁸ The Cystic Fibrosis Questionnaire-revised (CFQ-R) is a validated patient-reported outcome questionnaire specific to CF which focuses on health perception, quality of life, and clinically relevant respiratory symptoms. A minimally clinically important difference of 4 points was established for the respiratory symptom domain.²⁹ Change in body mass index (BMI) is also a commonly measured secondary outcome in trials of CF children, as studies have shown that lower than average birth weights and poor growth are correlated with decreased lung function, and increased morbidity and mortality.²⁹ The nutritional status of patients with CF is strongly associated with pulmonary function, respiratory status, and survival. Sweat chloride level is the gold standard for a diagnosis of CF. Normal individuals typically have levels less than 40 mmol/L, but patients with CF have elevated levels greater than 60 mmol/L.²⁸ More recently, endpoints such as sweat chloride, nasal potential difference, and the intestinal current measurement are proposed surrogate markers of CFTR function, as these reflect sodium absorption and chloride secretion dependent on CFTR function.¹⁹ Sweat chloride has been used as a biomarker for evaluation of change in CFTR activity in clinical trials of IVA.³⁰ Although initial studies showed a reduction in the sweat chloride levels to values below the diagnostic threshold for CF (60 mmol/L), there is no evidence that sweat chloride is correlated with meaningful clinical benefits, and it has not shown to correlate with improvement in FEV₁.²⁸ Clinical severity of CF is dependent on other factors in addition to CFTR function, and what aspect of CFTR function is affected depends on the specific combination of mutations in the individual.

FDA approved oral agents intended to enhance mutant CFTR protein function (CFTR modulators) are included in **Table 2**.³⁰ They include potentiators and correctors. CFTR potentiators increase the probability that the CFTR gene remains open, and correctors help to correct folding of the CFTR protein and its transportation to the cell surface. Ivacaftor (IVA) and deutivacaftor (D-IVA) are the only FDA approved CFTR potentiators and CFTR correctors include lumacaftor (LUM), tezacaftor (TEZ), elexacaftor (ELX), and vanzacaftor (VNZ). There are currently four FDA approved combination products (**Table 2**), and treatment depends on the specific CFTR genetic variants present. Triple therapy with ELX/TEZ/IVA has become standard of care for responsive variants and approximately 90% of persons with CF are eligible for treatment with triple therapy. In one head to head study, triple therapy with ELX/TEZ/IVA resulted in a larger improvement in pulmonary function and respiratory quality of life over 4 weeks compared to dual therapy with TEZ/IVA. Overall, triple therapy results in a more pronounced treatment effect compared to either dual therapy agent.^{9,24} Vanzacaftor/tezacaftor/deutivacaftor (VNZ/TEZ/D-IVA) has the same mechanism of action as ELX/TEZ/IVA and is FDA-indicated for 303 variants in the CFTR gene, representing over 90% of the U.S. population. Deutivacaftor is a novel CFTR potentiator that has been shown to have a reduced rate of clearance and a longer half-life compared with ivacaftor, thereby supporting once-daily dosing. For less common CFTR variants not feasible to enroll in clinical trials, CFTR modulators are FDA approved based on in vitro responsiveness data and extrapolation of efficacy data.

Table 2: CFTR Modulators: Summary of Studied Mutations

Generic Name (Brand)	FDA Approved Indication (in cystic fibrosis)
Ivacaftor ³¹ (Kalydeco [®])	≥ 1 months with an ivacaftor-responsive gene mutation, including G551D (Appendix 4)
Lumacaftor/ivacaftor ³² (Orkambi [®])	≥ 1 years Homozygous for F508del
Tezacaftor/ivacaftor ^{23,33} (Symdeko [®])	≥ 6 years who are homozygous for the F508del mutation OR who have at least one tezacaftor/ivacaftor-responsive CFTR mutation (Appendix 4)
Elexacaftor/tezacaftor/ivacaftor ³⁴ (Trikafta [®])	≥ 2 years who have at least one F508del mutation or another responsive mutation (Appendix 4)
Vanzacaftor/tezacaftor/deutivacaftor ³⁵ (Alyftrek)	≥ 6 years who have at least one F508del mutation or another responsive mutation

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canada’s Drug Agency (CDA-AMA), the Oregon Mental Health Clinical Advisory Group (MHCAG), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

After review, 4 systematic reviews were excluded due to poor quality^{36,37,37,38} (e.g, indirect network-meta analyses), wrong study design of included trials^{36,39,38} (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

- A Cochrane Collaboration systematic review was conducted to evaluate the effects of CFTR correctors (with or without potentiators) for people with CF with class II CFTR gene variants (most commonly F508del).² A total of 34 RCTs were included in the review (n=4781), including studies of monotherapy, dual therapy, and tripl therapy. All studies reported survival and 26 included quality of life on the respiratory domain of the CFQ-R.² Pharmaceutical companies funded 27 studies. Overall, there was low or unclear risk of bias in most domains with some studies having high risk of attrition bias and high risk of reporting bias due to selective outcome reporting. Overall, there was insufficient evidence to support monotherapy and limited evidence for dual therapy for individuals with CF and the F508del mutation. Studies evaluating triple therapy included ELX/TEZ/IVA and additional agents in combination with TEZ and IVA that are not currently FDA approved.² There were no deaths reported in studies evaluating triple therapy with. Compared to control, there is probably a benefit on quality of life respiratory domain scores with triple therapy and great absolute change in ppFEV1. There was moderate quality evidence of improved quality of life in the CFQ-R respiratory domain and improvement in absolute change in ppFEV1 (mean difference [MD] 14.3%; 95% CI 12.76 to

15.84) with triple therapy compared to placebo across all doses and genotypes. There was moderate quality evidence of no significant difference in adverse events between triple therapy and placebo control.

- A systematic review and meta-analysis following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework evaluated randomized controlled trials of ELX/TEZ/IVA in subjects with CF and at least one F508del mutation.³ The modified Cochrane risk of bias tool was used to assess risk of bias. A total of six studies were included in the meta-analysis comparing ELX/TEZ/IVA to active control (dual therapy with TEZ/IVA) or placebo. Most studies had low risk of bias, with the exception of one study having high risk of bias due to randomization and allocation concealment concerns. Studies reported no deaths, and therefore, it was not possible to assess the impact on survival. Meta analysis concluded low quality evidence of a improvement in respiratory domain quality of life (MD 14.93 points; 95% CI 9.98-19.89), an improvement in ppFEV1 (MD 10.47%; 95% CI 6.88 to 14.06), reduction in acute pulmonary exacerbations (MD -0.16; 95% CI -0.28 to -0.04) and moderate quality evidence of no significant difference in adverse events (81% vs. 84%; MD -0.03; 95% CI, -0.08 to 0.01).³

New Guidelines:

High Quality Guidelines:

National Institute for Health and Care Excellence (NICE) guidance on ELX/TEZ/IVA, TEZ/IVA, and LUM/IVA for treating cystic fibrosis⁹:

Based on a systematic review of available data, NICE concluded that symptomatic care for CF can be burdensome and does not treat the underlying condition. CFTR modulators are clinically effective, particularly in those with at least one F508del mutation. Overall, guidance recommends ELX/TEZ/IVA, TEZ/IVA, and LUM/IVA for routine use.

- ELX/TEZ/IVA is recommended as an option for treating CF in people 2 years and over who have at least one F508del mutation in the CFTR gene
- TEZ/IVA is recommended for CF in people 6 years and over who have:
 - 2 copies of the CFTR gene with F508del mutation, or
 - A copy of the CFTR gene with a F508del mutation and a copy of the CFTR gene with one other approved mutation
- LUM/IVA is recommended for CF in people one year and older who have 2 copies of the CFTR gene with F508del mutations

National Institute for Health and Care Excellence (NICE) guidance on Vanzacaftor-tezacaftor-deutivacaftor (VNZ/TEZ/D-IVA) for treating cystic fibrosis with 1 or more F508del mutations in the CFTR gene in people 6 years and over¹⁰:

NICE guidance concluded enough evidence to support benefits of VNZ/TEZ/D-IVA in patients 6 years and over with one or more F508del mutations in the CFTR gene.

- VNZ/TEZ/D-IVA can be used as an option to treat cystic fibrosis in people 6 years and over who have at least 1 F508del mutation in the CFTR gene
- Use the least expensive option of the suitable treatments (including VNZ/TEZ/D-IVA and ELX/TEZ/IVA), having discussed the advantages and disadvantages of the available treatments with the person with the condition

New Formulations or Indications:

- Ivacaftor (Kalydeco)⁴⁰:
 - 2020: FDA approved for pediatric patients age 4 months-to <6 months of age, and weighing ≥5 kg, who have at least one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data.
 - 2020: FDA approved for additional mutations in the CFTR gene that have been identified as responsive to ivacaftor based upon in vitro data.
 - 2023: FDA approved for patients 1 month to less than 4 months of age who have at least one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data, and adds dosages of 5.8 mg and 13.4 mg granules
- Lumacaftor/ivacaftor (Orkambi)³²:
 - 2022: FDA approved for children with CF ages 12 to 24 months who are homozygous for the F508del mutation
- Elexacaftor/tezacaftor/ivacaftor (Trikafta)³⁴
 - 2024: FDA approved for additional 94 non-F508del responsive variants based on in vitro data

New FDA Safety Alerts:

In December 2024, the safety warning on drug induced liver injury and liver failure associated with ELX/TEZ/IVA was updated from a warning and precaution to a boxed warning. ELZ/TEZ/IVA can cause serious and potentially fatal drug-induced liver injury. Liver function should be monitored at baseline, every month for the first 6 months, then every 3 months for the next 12 months, then at least annually.

Table 1. Description of New FDA Safety Alerts³⁴

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Elexacaftor/tezacaftor/ivacaftor	Trikafta	December 2024	Boxed Warning	Warning and precaution of drug induced liver injury and liver failure was updated to a boxed warning

Randomized Controlled Trials:

A total of 12 citations were manually reviewed from the initial literature search. After further review, 7 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). Two trials evaluating VNZ/TEZ/D-IVA are summarized in the new drug evaluation, and the remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Sutharsan et al. ⁴	1. ELX/TEZ/IVA 200 mg/ 100 mg/150 mg QAM + IVA 150 mg QPM vs. (n=87) 2. TEZ 100 mg QAM + IVA 150 mg BID (n=88)	≥ 12 yo with CF homozygous for the F508del-CFTR mutation, with a ppFEV1 of 40–90%	absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline at week 24	1: 17.1 points 2: 1.2 points LSM treatment difference 15.9 points (95% CI 11.7 to 20.1) p<0.0001	ELZ/TEZ/IVA also resulted in a statistically significant improvement in ppFEV1 from baseline compared to TEZ/IVA
Barry et al. ¹	1. ELX/TEZ/IVA (n=132) 2. active control* (IVA or TEZ/IVA) (n=126) <i>*with regimen from run-in period</i>	≥ 12 yo with CF and Phe508del-gating or Phe508del-residual function genotypes	absolute change in the ppFEV ₁ from baseline through week 8	1. 3.7% 2. 0.2% Difference 3.5% (95% CI 2.2 to 4.7); p<0.001	<ul style="list-style-type: none"> designed by Vertex Pharmaceuticals 4-week run-in period Small change in ppFEV₁ may not represent a clinically meaningful difference
McKone et al. ⁸	1. TEZ 100 mg QAM + IVA 150 mg Q12h (n=76) 2. IVA 150 mg Q12H (n=75)	≥12 yo with CF, heterozygous for the F508del-CFTR mutation and a CFTR mutation with a gating defect that was responsive to IVA, ppFEV1 of 40 to 90%	absolute change from baseline in ppFEV1 through Week 8	1. 0.5% 2. 0.2% Difference 0.3% (95% CI -0.8 to 1.4); p=0.58	<ul style="list-style-type: none"> 4-week run-in period with IVA 19% of subjects had a R117H gating mutation TEZ/IVA did not lead to clinically meaningful benefits over IVA alone in participants with a gating genotype

Abbreviations: CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; ELX/TEZ/IVA: Elexacaftor/tezacaftor/ivacaftor; IVA = ivacaftor; LSM = least squares mean; ppFEV1 = Percent predicted forced expiratory volume; TEZ: tezacaftor

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Vanzacaftor/tezacaftor/deutivacaftor (VNZ/TEZ/D-IVA) was FDA approved based on two multicenter, randomized, active-controlled, noninferiority, phase 3 trials that were simiilary designed. ⁷ Study 102 included subjects with F508del-minimal function genotypes and study 103 included subjects with those homozygous for F508del, F508del-residual function, F5-8del-gating, or ELX/TEZ/IVA-responsive non-F508del genotypes. All patients received ELX/TEZ/IVA during a 4-week run-in period, and patients who tolerated the run-in period were randomized to VNZ/TEZ/D-IVA or ELX/TEZ/IVA for a 52 week treatment period. The primary outcome in both trials was absolute change in ppFEV1 from baseline through week 24 (estimated by averaging week 16 and 24). Non-inferiority was demonstrated if the lower bound of the 95% CI was -3.0 percentage points or greater. Among the enrolled population, 95.7% of subject had a CFTR genotype that included at least one copy of the F508del variant, the most common variant in the U.S. CF population. Most (87%) participants reported prior use of ELX/TEZ/IVA, and overall these studies included a stable CF population with higher ppFEV1 at baseline and lower sweat chloride than previous studies of CF modulators.

In study 102, of the 488 screened, 435 participants entered the run-in period and 398 were randomized to study treatment. The least squares mean absolute change in ppFEV1 from baseline through week 24 was 0.5% (SE 0.3) in VNZ/TEZ/D-IVA versus 0.3% (0.3) in ELX/TEZ/IVA (least squares mean treatment difference of 0.2% [95% CI -0.7 to 1.1]; one-sided $p < 0.0001$). In study 103, of the 699 screened 597 participants entered the run-in period, and 573 were randomized to study treatment. The least squares mean absolute change in ppFEV1 from baseline through week 24 was 0.2% (SE 0.3) in VNZ/TEZ/IVA versus 0.0% (SE 0.2) in ELX/TEZ/IVA (least squares mean treatment difference of 0.2% [95% CI -0.5 to 0.9]; one-sided $p < 0.0001$). Most participants (77.8%) were homozygous for F508del. Both trials demonstated the non-inferiority of VNZ/TEZ/D-IVA to ELX/TEZ/IVA for ppFEV1 through 24 weeks. There were similar and overall very low rates of pulmonary exacerbations in both treatment groups.

Approximately 85% of participants in both studies were adults 18 years and older. In the subgroup analysis of the adolescent group in Study 102, the LS mean difference of the ppFEV1 between VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatment groups was 1.3% (95% CI -3.9% to 1.3%), with the lower bound of the 95% CI smaller than the noninferiority margin of -3.0%. Interpretation of results in the adolescent subgroup is limited because of the small sample size and more data is needed to confirm efficacy and safety. In Study 103, the subgroup analysis in the adolescent group was consistent with the overall population (LS mean difference 0.9% (95% CI -1.2% to 3%), despite the small sample size. The efficacy of VNZ/TEZ/D-IVA was extrapolated to patients aged 6 to 11 years of age and an exploratory data from an open-label trial demonstrating comparable systemic exposure.^{41,42} For additional and less common variants, approval was based on in vitro data submitted to the FDA to support the inclusion of a total of 303 CFTR variants in the indication of VNZ/TEZ/D-IVA.

Clinical Safety:

In the two pivotal RCTs comparing VNZ/TEZ/D-IVA to ELX/TEZ/IVA, rates of discontinuations due to adverse events were low and similar between the two groups (3.8% and 3.7%, respectively). Across both trials, the majority of subjects in each group (96%) experienced at least one adverse event. Most were mild to moderate in severity and resolved with treatment interruption. Common adverse reactions that were similar in both treatment groups included: infective pulmonary exacerbations, diarrhea, abdominal pain, nasal congestion, rhinorreha, back pain, arthralgia, constipation, and vomiting. Common adverse events that occurred more frequently with VNZ/TEZ/D-IVA are included below (**Table 3**). Serious adverse events occurred in 16% of ELX/TEZ/IVA subjects and 14% of VNZ/TEZ/D-IVA subjects.

Table 3: Adverse reactions occurring in ≥ 5% of patients and higher than ELX/TEZ/IVA:

Adverse Reactions	vanzacaftor/tezacaftor/deutivacaftor (Alyftrek) n=480	elexacaftor/tezacaftor/ivacaftor (Trikafta) n=491
Cough	120 (25%)	116 (24%)
Nasopharyngitis	102 (21%)	95 (19%)
Upper respiratory tract infection	101 (21%)	97 (20%)
Headache	76 (16%)	63 (13%)
Oropharyngeal pain	69 (14%)	60 (12%)
Influenza	52 (11%)	26 (5%)
Fatigue	51 (11%)	46 (9%)
ALT increased	38 (8%)	29 (6%)
Rash	37 (8%)	22 (4%)
AST increased	33 (7%)	27 (5%)

The safety profile of VNZ/TEZ/D-IVA appears similar to that of ELX/TEZ/IVA and includes the potential risk for drug induced liver injury and liver failure. A Boxed Warning for drug-induced liver injury and liver failure is included in labeling. Liver function should be assessed at baseline, every month during the first 6 months, ever 3 months for the next 12 months, then at least annually. Treatment should be interrupted in the event of signs or symptoms of liver injury and use is not recommended in patients with severe hepatic impairment. In the trials, 1.5% of subjects on VNZ/TEZ/D-IVA and 0.6% of ELX/TEZ/IVA discontinued due to elevated liver transaminases. Safety for the 6- through 11-year-old CF population was extrapolated from the adolescent and adult populations enrolled in the phase 3 development program based upon comparable systemic exposures. VNZ/TEZ/D-IVA is metabolized by CYP3A4 and use of moderate to strong inducers or inhibitors should be avoided.

Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Survival
- 2) Quality of life
- 3) Pulmonary exacerbations
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Absolute change in FEV1 percent predicted from ELX/TEZ/IVA baseline through week 24 (estimated by average week 16 and 24)

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Keating, et al. VS20-121-102 Phase 3, AC, MC, NI, RCT	1. ELX/TEZ/IVA 200mg/100 mg/150 QAM + IVA 150 mg QPM	<u>Demographics:</u> <ul style="list-style-type: none"> • 41% female • Median age 31 • 98% white • ppFEV₁ 67% 	<u>ITT:</u> 1. 202 2. 196 <u>PP:</u> 1. 186	<u>Primary Endpoint:</u> Absolute change in ppFEV1 from baseline to week 24: 1. 0.3% 2. 0.5%	N/A	<u>Discontinuations due to adverse effects:</u> 1. 10 (5.0%) 2. 4 (2%)	N/A	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> low; randomized using generated random code list and interactive web-response system. Groups similar at baseline.

	<p>2. VNZ/TEZ/D-IVA 20 mg/100 mg/250 mg QAM</p>	<ul style="list-style-type: none"> Previous CFTR 87% <p><u>Key Inclusion Criteria:</u></p> <ul style="list-style-type: none"> ≥ 12 years, FEV₁ 40-80% not on ELX/TEZ/IVA or 40-90% on ELX/TEZ/IVA, Heterozygous for F508del and a MF mutation <p><u>Key Exclusion Criteria:</u></p> <ul style="list-style-type: none"> Severe hepatic impairment Alcohol or drug abuse Cancer Hg < 10 g/dl Bilirubin > 2 x ULN AST/ALT > 3 x ULN eGFR ≤ 50 ml/min pregnant or breastfeeding 	<p>2. 181</p> <p><u>Attrition:</u></p> <p>1. 16</p> <p>2. 15</p>	<p>LSM difference 0.2% (95%CI -0.7 to 1.1) P<0.0001*</p> <p>*p for non-inferiority</p> <p><u>Secondary Endpoints***:</u> Absolute change in CFQ-R respiratory domain at week 24:</p> <p>1. -1.7 2. 0.5 LSM difference 2.3 (-0.6, 5.2)</p> <p>Number of pulmonary exacerbations through week 52 (annual event rate):</p> <p>1. 0.42 2. 0.32 Rate difference -0.10 (-0.24, 0.04)</p> <p>***the interpretation of these endpoints is limited because they were analyzed without control for multiplicity.</p>	<p>N/A</p> <p>N/A</p>	<p>*p values not provided</p>	<p><u>Performance Bias:</u> low; all participants site personnel, and study team were blinded to treatment group; matched placebo tablets in size and appearance used.</p> <p><u>Detection Bias:</u> unclear; unclear blinding of outcome assessors</p> <p><u>Attrition Bias:</u> low; mITT used for efficacy analysis. Low attrition and similar between groups.</p> <p><u>Reporting Bias:</u> unclear</p> <p><u>Other Bias:</u> The trial sponsor (Vertex Pharmaceuticals) had a role in the design, data analysis, data interpretation, and writing of the report.</p> <p><u>Applicability:</u> <u>Patient:</u> : Extensive exclusion criteria limits generalizability including significant comorbidity left up to the discretion of the provider, limited subjects included with severe disease (FEV₁ < 40%) or with FEV₁ > 90%, screening and run in periods limits applicability and few patients < 18 yo. Limited generalizability to ELX/TEZ/IVA naïve or intolerant patients.</p> <p><u>Intervention:</u> triple therapy with similar mechanism to comparator, but longer acting D-IVA allows for once daily dosing. Highest dose selected based on phase 2 dose response studies.</p> <p><u>Comparator:</u> placebo was determined to be unethical. ELX/TEZ/IVA is standard of care and is an appropriate active control for the study</p> <p><u>Outcomes:</u> FEV₁ is a surrogate outcome. There is no agreed upon difference clinically meaningful difference and it has not been established that changes in FEV₁ translate to long term clinical benefits.</p> <p><u>Setting:</u> 126 sites in Australia, Czech Republic, Germany, Hungary, Ireland, Israel, New Zealand, Portugal, Spain, Sweden, UK, and USA</p>
<p>2. VS20-121-103 Phase 3, AC, MC, NI, RCT</p>	<p>1. ELX/TEZ/IVA 200mg/100 mg/150 mg QAM + IVA 150 mg QPM</p>	<p><u>Demographics:</u></p> <ul style="list-style-type: none"> 49% female Median age 33 93% white ppFEV₁ 67% Previous CFTR modulator 86% 	<p><u>ITT:</u></p> <p>1. 289</p> <p>2. 284</p> <p><u>PP:</u></p> <p>1. 273</p> <p>2. 259</p>	<p><u>Primary Endpoint:</u> Absolute change in ppFEV₁ from baseline to week 24:</p> <p>1. 0.0</p> <p>2. 0.2%</p>	<p>N/A</p>	<p><u>Discontinuations due to adverse effects:</u></p> <p>1. 9 (3.1%)</p> <p>2. 14 (4.9%)</p>	<p><u>Risk of Bias (low/high/unclear):</u> <u>Selection Bias:</u> low; randomized using generated random code list and interactive web-response system. Groups similar at baseline.</p> <p><u>Performance Bias:</u> low; all participants site personnel, and study team were blinded to treatment group; matched placebo tablets in size and appearance used.</p>

	<p>2. VNZ/TEZ/D-IVA 20 mg/100 mg/250 mg QAM</p>	<ul style="list-style-type: none"> F508del-F508del mutation: 78% <p><u>Key Inclusion Criteria:</u></p> <ul style="list-style-type: none"> ≥ 12 years, FEV₁ 40-80% not on CFTR modulator or 40-90% on CFTR modulator, Homozygous for F508del, F508del-residual function, F508del-gating, or ELX/TEZ/IVA responsive-non-F508del genotypes <p><u>Key Exclusion Criteria:</u> Same as study above</p>	<p><u>Attrition:</u></p> <ol style="list-style-type: none"> 16 25 	<p>LSM difference 0.2% (95%CI -0.5 to -0.9) P<0.0001*</p> <p>*p for non-inferiority</p> <p><u>Secondary Endpoints***:</u> Absolute change in CFQ-R respiratory domain at week 24:</p> <ol style="list-style-type: none"> -1.2 -1.2 <p>LSM difference -0.1 (95% CI -2.3, 2.1)</p> <p>Number of pulmonary exacerbations through week 52 (annual event rate):</p> <ol style="list-style-type: none"> 0.26 0.29 <p>Rate difference 0.03 (95% CI -0.07, 0.13)</p> <p>***the interpretation of these endpoints is limited because they were analyzed without control for multiplicity.</p>	<p>N/A</p> <p>N/A</p> <p>N/A</p>	<p>*p values not included</p>	<p><u>Detection Bias:</u> unclear; unclear blinding of outcome assessors <u>Attrition Bias:</u> low; mITT used for efficacy analysis. Low attrition and similar between groups. <u>Reporting Bias:</u> unclear <u>Other Bias:</u> The trial sponsor (Vertex Pharmaceuticals) had a role in the design, data analysis, data interpretation, and writing of the report.</p> <p>Applicability: <u>Patient:</u> Extensive exclusion criteria limits generalizability including significant comorbidity left up to the discretion of the provider, limited subjects included with severe disease (FEV₁ < 40%) or with FEV₁ > 90%, screening and run in periods limits applicability and few patients < 18 yo. Limited generalizability to ELX/TEZ/IVA naïve or intolerant patients. <u>Intervention:</u> triple therapy with similar mechanism to comparator, but longer acting D-IVA allows for once daily dosing. Highest dose selected based on phase 2 dose response studies. <u>Comparator:</u> placebo was determined to be unethical. ELX/TEZ/IVA is standard of care and is an appropriate active control for the study <u>Outcomes:</u> FEV₁ is a surrogate outcome. There is no agreed upon difference clinically meaningful difference and it has not been established that changes in FEV₁ translate to long term clinical benefits. <u>Setting:</u> 159 sites in Australia, Austria, Belgium, Canada, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Netherlands, New Zealand, Norway, oland, Sweden Switzerland, the UK, and USA</p>
<p>Abbreviations [alphabetical order]: AC = active control; ALT = alanine aminotransferase; ARR = absolute risk reduction; AST = aspartate aminotransferase; CI = confidence interval; CFQ-R = The Cystic Fibrosis Questionnaire-Revised; CFTR = cystic fibrosis transmembrane conductance regulator; eGFR = estimated glomerular filtration rate; ELX/TEZ/IVA = Elexacaftor/tezacaftor/ivacaftor; Hg = hemoglobin; ITT = intention to treat; LSM = least square mean; MC = multicenter; MF: minimal function; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NI = noninferiority; NNH = number needed to harm; LSM: least squares mean; NNT = number needed to treat; PP = per protocol; ppFEV₁ = Percent predicted forced expiratory volume; RCT = randomized controlled trial; VNZ/TEZ/D-IVA = Vanzacaftor/tezacaftor/deutivacaftor; ULN = upper limit of normal</p>							

Table 5. Pharmacology and Pharmacokinetic Properties.

Parameter			
Mechanism of Action	VNZ and TEZ bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of select mutant forms of CFTR (including F508del-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. D-IVA potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.		
	VNZ	TEZ	D-IVA
Oral Bioavailability	N/A	N/A	N/A
Distribution	121 L	73.1 L	D-IVA:
Protein Binding	>99%	99%	>99%
Half-Life	92.8 h	22.5 h	19.2 h
Metabolism	Primarily via CYP3A4/5.	Primarily via CYP3A4/5 to active metabolite M1-TEZ (similar potency to parent compound).	Primarily via CYP3A4/5 to active metabolite M1-D-IVA (~20% potency compared to parent compound).
Excretion	Urine (0.5%); feces (91.6% as primarily metabolites)	Urine (13.7%); feces (72% as unchanged drug or M2-TEZ metabolite)	N/A

Abbreviations: CFTR: cystic fibrosis transmembrane conductance regulator; D-IVA: deutivacaftor; TEZ: tezacaftor; VNZ: vanzacaftor

References:

1. Barry PJ, Mall MA, Álvarez A, et al. Triple Therapy for Cystic Fibrosis Phe508del-Gating and -Residual Function Genotypes. *The New England journal of medicine*. Aug 26 2021;385(9):815-825. doi:10.1056/NEJMoa2100665
2. Heneghan M, Southern KW, Murphy J, Sinha IP, Nevitt SJ. Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del). *Cochrane Database Syst Rev*. Nov 20 2023;11(11):Cd010966. doi:10.1002/14651858.CD010966.pub4
3. Silva Filho L, Athanazio RA, Tonon CR, Ferreira JC, Tanni SE. Use of elexacaftor+tezacaftor+ivacaftor in individuals with cystic fibrosis and at least one F508del allele: a systematic review and meta-analysis. *J Bras Pneumol*. 2024;49(6):e20230187. doi:10.36416/1806-3756/e20230187
4. Sutharsan S, McKone EF, Downey DG, et al. Efficacy and safety of elexacaftor plus tezacaftor plus ivacaftor versus tezacaftor plus ivacaftor in people with cystic fibrosis homozygous for F508del-CFTR: a 24-week, multicentre, randomised, double-blind, active-controlled, phase 3b trial. *The Lancet Respiratory medicine*. Mar 2022;10(3):267-277. doi:10.1016/s2213-2600(21)00454-9
5. McGarry ME, Gibb ER, Oates GR, Schechter MS. Left behind: The potential impact of CFTR modulators on racial and ethnic disparities in cystic fibrosis. *Paediatr Respir Rev*. Jun 2022;42:35-42. doi:10.1016/j.prrv.2021.12.001
6. Wu M, Davis JD, Zhao C, Daley T, Oliver KE. Racial inequities and rare CFTR variants: Impact on cystic fibrosis diagnosis and treatment. *J Clin Transl Endocrinol*. Jun 2024;36:100344. doi:10.1016/j.jcte.2024.100344
7. Keating C, Yonker LM, Vermeulen F, et al. Vanzacaftor-tezacaftor-deutivacaftor versus elexacaftor-tezacaftor-ivacaftor in individuals with cystic fibrosis aged 12 years and older (SKYLINE Trials VX20-121-102 and VX20-121-103): results from two randomised, active-controlled, phase 3 trials. *The Lancet Respiratory medicine*. Mar 2025;13(3):256-271. doi:10.1016/s2213-2600(24)00411-9
8. McKone EF, DiMango EA, Sutharsan S, et al. A phase 3, randomized, double-blind, parallel-group study to evaluate tezacaftor/ivacaftor in people with cystic fibrosis heterozygous for F508del-CFTR and a gating mutation. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. Mar 2021;20(2):234-242. doi:10.1016/j.jcf.2020.11.003
9. National institute for Health and Clinical Excellence (NICE): Ivacaftor-tezacaftor-elexacaftor, tezacaftor-ivacaftor and lumacaftor-ivacaftor for treatment cystic fibrosis. Technology appraisal guidance. July 24 2024. Available at: <https://www.nice.org.uk/guidance/ta988>.
10. National institute for Health and Clinical Excellence (NICE): Vanzacaftor-tezacaftordeutivacaftor for treating cystic fibrosis with 1 or more F508del mutations in the CFTR gene in people 6 years and over . July 30 2025. Available at: <https://www.nice.org.uk/guidance/ta1085>.
11. Southern KW, Patel S, Sinha IP, Nevitt SJ. Correctors (specific therapies for class II CFTR mutations) for cystic fibrosis. *Cochrane Database Syst Rev*. Aug 2 2018;8:Cd010966. doi:10.1002/14651858.CD010966.pub2
12. Tice JA, Kuntz KM, Wherry K, Chapman R, Seidner M, Pearson SD, Rind DM. Modulator Treatments for Cystic Fibrosis: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, April 27, 2020. <https://icer-review.org/material/cystic-fibrosis-2-evidence-report/>.
13. Skilton M, Krishan A, Patel S, Sinha IP, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *Cochrane Database Syst Rev*. Jan 7 2019;1:Cd009841. doi:10.1002/14651858.CD009841.pub3
14. Middleton PG, Mall MA, Drevinek P, et al. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *The New England journal of medicine*. Nov 7 2019;381(19):1809-1819. doi:10.1056/NEJMoa1908639

15. Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet (London, England)*. Nov 23 2019;394(10212):1940-1948. doi:10.1016/s0140-6736(19)32597-8
16. Whiting P, Al M, Burgers L, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. *Health technology assessment (Winchester, England)*. Mar 2014;18(18):1-106. doi:10.3310/hta18180
17. Mogayzel PJ, Jr., Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *American journal of respiratory and critical care medicine*. Apr 1 2013;187(7):680-9.
18. Kumar S, Tana A, Shankar A. Cystic fibrosis--what are the prospects for a cure? *European journal of internal medicine*. Nov 2014;25(9):803-7. doi:10.1016/j.ejim.2014.09.018
19. O'Reilly R, Elphick HE. Development, clinical utility, and place of ivacaftor in the treatment of cystic fibrosis. *Drug design, development and therapy*. 2013;7:929-37. doi:10.2147/dddt.s30345
20. Grasemann H, Ratjen F. Cystic Fibrosis. *The New England journal of medicine*. Nov 2 2023;389(18):1693-1707. doi:10.1056/NEJMra2216474
21. Moss RB, Flume PA, Elborn JS, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an Arg117His-CFTR mutation: a double-blind, randomised controlled trial. *The Lancet Respiratory medicine*. Jul 2015;3(7):524-33. doi:10.1016/s2213-2600(15)00201-5
22. Flume PA, Liou TG, Borowitz DS, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest*. Sep 2012;142(3):718-724. doi:10.1378/chest.11-2672
23. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. *The New England journal of medicine*. Nov 23 2017;377(21):2024-2035. doi:10.1056/NEJMoa1709847
24. Tice JA, Kuntz KM, Wherry K, Chapman R, Seidner M, Pearson SD, Rind DM. Modulator Treatments for Cystic Fibrosis: Effectiveness and Value; Final Evidence Report and Meeting Summary. Institute for Clinical and Economic Review, September 23, 2020. <https://icerreview.org/material/cystic-fibrosis-2-final-evidence-report-and-meeting-summary/>
25. Food and Drug Administration Center for Drug Evaluation and Research. Application Number: 212273Orig1s000. Multi-disciplinary review and evaluation. Trifakta, elexacaftor/tezacaftor/ivacaftor. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212273Orig1s000TOC.cfm.
26. National Institute for Health and Care Excellence (NICE). Lumacaftor-ivacaftor for treating cystic fibrosis homozygous for the F508del mutation. Technology appraisal guidance. Published: July 27 2016. Available at: www.nice.org.uk/guidance/ta398.
27. Liou TG, Elkin EP, Pasta DJ, et al. Year-to-year changes in lung function in individuals with cystic fibrosis. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. Jul 2010;9(4):250-6. doi:10.1016/j.jcf.2010.04.002
28. Durmowicz AG, Witzmann KA, Rosebraugh CJ, Chowdhury BA. Change in sweat chloride as a clinical end point in cystic fibrosis clinical trials: the ivacaftor experience. *Chest*. Jan 2013;143(1):14-18. doi:10.1378/chest.12-1430
29. Quittner AL, Modi AC, Wainwright C, Otto K, Kirihara J, Montgomery AB. Determination of the minimal clinically important difference scores for the Cystic Fibrosis Questionnaire-Revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic *Pseudomonas aeruginosa* airway infection. *Chest*. Jun 2009;135(6):1610-1618. doi:10.1378/chest.08-1190
30. Mayer-Hamblett N, Boyle M, VanDevanter D. Advancing clinical development pathways for new CFTR modulators in cystic fibrosis. *Thorax*. May 2016;71(5):454-61. doi:10.1136/thoraxjnl-2015-208123

31. Vertex Pharmaceuticals. Kalydeco (ivacaftor) Prescribing Information. May 2017. http://pi.vrtx.com/files/uspi_ivacaftor.pdf. Accessed November 5, 2017.
32. Orkambi Prescribing Information. Prescribing Information. Vertex Pharmaceuticals. Boston, MA 02210. December 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/206038s018,211358s0061bl.pdf.
33. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *The New England journal of medicine*. Nov 23 2017;377(21):2013-2023. doi:10.1056/NEJMoa1709846
34. Trikafta Prescribing Information. Vertex Pharmaceuticals. Boston, MA. December 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/212273Orig1s013;217660Orig1s005corrected1bl.pdf.
35. Alyftrek Prescribing Information. Vertex Pharmaceuticals. Boston, MA 02210. December 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218730s0001bl.pdf.
36. Edwards SJ, Farrar BG, Ennis K, et al. Ivacaftor-tezacaftor-elexacaftor, tezacaftor-ivacaftor and lumacaftor-ivacaftor for treating cystic fibrosis: a systematic review and economic evaluation. *Health technology assessment (Winchester, England)*. May 2025;29(19):1-111. doi:10.3310/cpld8546
37. Iftikhar IH, Rao ST, Nadama R, Janahi I, BaHammam AS. Comparative Efficacy of CFTR Modulators: A Network Meta-analysis. *Lung*. Mar 18 2025;203(1):49. doi:10.1007/s00408-025-00802-w
38. Gramegna A, Contarini M, Aliberti S, Casciaro R, Blasi F, Castellani C. From Ivacaftor to Triple Combination: A Systematic Review of Efficacy and Safety of CFTR Modulators in People with Cystic Fibrosis. *Int J Mol Sci*. Aug 16 2020;21(16)doi:10.3390/ijms21165882
39. Lupas D, Chou FY, Hakani MAA, et al. The clinical effectiveness of elexacaftor/tezacaftor/ivacaftor (ETI) for people with CF without a F508del variant: A systematic review and meta-analysis. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*. Sep 2024;23(5):950-958. doi:10.1016/j.jcf.2024.07.012
40. Vertex Pharmaceuticals. Kalydeco (ivacaftor) Prescribing Information. May 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/203188s041,207925s0191bl.pdf.
41. FDA Center for Drug Evaluation and Research. vanzacaftor/tezacaftor/deutivacaftor Integrated Review. Application Number: 218730Orig1s000 . Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/218730Orig1s000IntegratedR.pdf.
42. Hoppe JE, Kasi AS, Pittman JE, et al. Vanzacaftor-tezacaftor-deutivacaftor for children aged 6-11 years with cystic fibrosis (RIDGELINE Trial VX21-121-105): an analysis from a single-arm, phase 3 trial. *The Lancet Respiratory medicine*. Mar 2025;13(3):244-255. doi:10.1016/s2213-2600(24)00407-7

Appendix 1: Current Preferred Drug List*

<u>Generic</u>	<u>Generic</u>	<u>Route</u>	<u>Form</u>	<u>PDL</u>
tobramycin in 0.225% sod chlor	tobramycin in 0.225% sod chlor	INHALATION	AMPUL-NEB	Y
tobramycin in 0.225% sod chlor	tobramycin in 0.225% sod chlor	INHALATION	AMPUL-NEB	Y
dornase alfa	dornase alfa	INHALATION	SOLUTION	Y
sodium chloride for inhalation	sodium chloride for inhalation	INHALATION	VIAL-NEB	Y
sodium chloride for inhalation	sodium chloride for inhalation	INHALATION	VIAL-NEB	Y
tobramycin	tobramycin	INHALATION	AMPUL-NEB	N
tobramycin	tobramycin	INHALATION	AMPUL-NEB	N
tobramycin	tobramycin	INHALATION	CAP W/DEV	N
aztreonam lysine	aztreonam lysine	INHALATION	VIAL-NEB	N
tobramycin/nebulizer	tobramycin/nebulizer	INHALATION	AMPUL-NEB	N
tobramycin/nebulizer	tobramycin/nebulizer	INHALATION	AMPUL-NEB	N
amikacin liposomal/neb.accessr	amikacin liposomal/neb.accessr	INHALATION	VIAL-NEB	N
mannitol	mannitol	INHALATION	CAP W/DEV	N
ivacaftor	ivacaftor	ORAL	GRAN PACK	N
lumacaftor/ivacaftor	lumacaftor/ivacaftor	ORAL	GRAN PACK	N
elexacaftor/tezacaftor/ivacaft	elexacaftor/tezacaftor/ivacaft	ORAL	GRAN PK SQ	N
ivacaftor	ivacaftor	ORAL	TABLET	N
lumacaftor/ivacaftor	lumacaftor/ivacaftor	ORAL	TABLET	N
tezacaftor/ivacaftor	tezacaftor/ivacaftor	ORAL	TABLET SEQ	N
elexacaftor/tezacaftor/ivacaft	elexacaftor/tezacaftor/ivacaft	ORAL	TABLET SEQ	N
vanzacaftor/tezacaf/deutivacaf	vanzacaftor/tezacaf/deutivacaf	ORAL	TABLET	N

*Class update limited to oral modulators

Appendix 2: Abstracts of Comparative Clinical Trials

Sutharsan S, McKone EF, Downey DG, et al. Efficacy and safety of elexacaftor plus tezacaftor plus ivacaftor versus tezacaftor plus ivacaftor in people with cystic fibrosis homozygous for F508del-CFTR: a 24-week, multicentre, randomised, double-blind, active-controlled, phase 3b trial. *Lancet Respir Med*. 2022;10(3):267-277. doi:10.1016/S2213-2600(21)00454-9

Background: Elexacaftor plus tezacaftor plus ivacaftor is a triple-combination cystic fibrosis transmembrane conductance regulator (CFTR) modulator regimen shown to be generally safe and efficacious in people with cystic fibrosis aged 12 years or older with at least one F508del-CFTR allele. We aimed to assess the magnitude and durability of the clinical effects of this triple combination regimen in people with cystic fibrosis homozygous for the F508del-CFTR mutation.

Methods: We conducted a multicentre, randomised, double-blind, active-controlled, phase 3b trial of elexacaftor plus tezacaftor plus ivacaftor at 35 medical centres in Australia, Belgium, Germany, and the UK. Eligible participants were those with cystic fibrosis homozygous for the F508del-CFTR mutation, aged 12 years or older with stable disease, and with a percent predicted FEV₁ of 40-90% inclusive. After a 4-week run-in period, in which participants received tezacaftor 100 mg orally once daily and ivacaftor 150 mg orally every 12 h, participants were randomly assigned (1:1) to receive 24 weeks of either elexacaftor 200 mg orally once daily plus tezacaftor 100 mg orally once daily plus ivacaftor 150 mg orally every 12 h (elexacaftor plus tezacaftor plus ivacaftor group) or tezacaftor 100 mg orally once daily plus ivacaftor 150 mg orally every 12 h (tezacaftor plus ivacaftor group). Randomisation was stratified by percent predicted FEV₁, age at screening visit, and whether the participant was receiving CFTR modulators at the time of the screening visit. Patients, investigators, and sponsor's study execution team were masked to treatment assignment. The primary endpoint was the absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline (ie, at the end of the tezacaftor plus ivacaftor run-in period) up to and including week 24. The key secondary endpoint was the absolute change from baseline in percent predicted FEV₁ up to and including week 24; other secondary endpoints were the absolute change from baseline in sweat chloride concentrations up to and including week 24, and safety and tolerability. All endpoints were assessed in all randomised patients who had received at least one dose of their assigned regimen. This study is registered with ClinicalTrials.gov, [NCT04105972](https://clinicaltrials.gov/ct2/show/study/NCT04105972).

Findings: Between Oct 3, 2019, and July 24, 2020, 176 participants were enrolled. Following the 4-week tezacaftor plus ivacaftor run-in period, 175 participants were randomly assigned (87 to the elexacaftor plus tezacaftor plus ivacaftor group and 88 to the tezacaftor plus ivacaftor group) and dosed in the treatment period. From baseline up to and including week 24, the mean CFQ-R respiratory domain score increased by 17·1 points (95% CI 14·1 to 20·1) in the elexacaftor plus tezacaftor plus ivacaftor group and by 1·2 points (-1·7 to 4·2) in the tezacaftor plus ivacaftor group (least squares mean treatment difference 15·9 points [95% CI 11·7 to 20·1], p<0·0001), the mean percent predicted FEV₁ increased by 11·2 percentage points (95% CI 9·8 to 12·6) in the elexacaftor plus tezacaftor plus ivacaftor group and by 1·0 percentage points (-0·4 to 2·4) in the tezacaftor plus ivacaftor group (least squares mean treatment difference 10·2 percentage points [8·2 to 12·1], p<0·0001), and the mean sweat chloride concentration decreased by 46·2 mmol/L (95% CI 43·7 to 48·7) in the elexacaftor plus tezacaftor plus ivacaftor group and by 3·4 mmol/L (1·0 to 5·8) in the tezacaftor plus ivacaftor group (least squares mean treatment difference -42·8 mmol/L [-46·2 to -39·3], nominal p<0·0001). Most participants (70 [80%] in the elexacaftor plus tezacaftor plus ivacaftor group and 74 [84%] in the tezacaftor plus ivacaftor group) had adverse events that were mild or moderate in severity; serious adverse events occurred in five (6%) of 87 participants in the elexacaftor plus tezacaftor plus ivacaftor group and 14 (16%) of 88 participants in the tezacaftor plus ivacaftor group. One (1%) participant in the elexacaftor plus tezacaftor plus ivacaftor group discontinued treatment due to an adverse event of anxiety and depression. Two (2%) participants in the tezacaftor plus ivacaftor group discontinued treatment due to adverse events of psychotic disorder (n=1) and obsessive-compulsive disorder (n=1).

Interpretation: The elexacaftor plus tezacaftor plus ivacaftor regimen was safe and well tolerated, and led to significant and clinically meaningful improvements in respiratory-related quality of life and lung function, as well as improved CFTR function, changes that were durable over 24 weeks and superior to those seen with tezacaftor plus ivacaftor in this patient population.

Funding: Vertex Pharmaceuticals.

Barry PJ, Mall MA, Álvarez A, et al. Triple Therapy for Cystic Fibrosis *Phe508del*-Gating and -Residual Function Genotypes. *N Engl J Med.* 2021;385(9):815-825. doi:10.1056/NEJMoa2100665

Background: Elexacaftor-tezacaftor-ivacaftor is a small-molecule cystic fibrosis transmembrane conductance regulator (CFTR) modulator regimen shown to be efficacious in patients with at least one *Phe508del* allele, which indicates that this combination can modulate a single *Phe508del* allele. In patients whose other *CFTR* allele contains a gating or residual function mutation that is already effectively treated with previous CFTR modulators (ivacaftor or tezacaftor-ivacaftor), the potential for additional benefit from restoring *Phe508del* CFTR protein function is unclear.

Methods: We conducted a phase 3, double-blind, randomized, active-controlled trial involving patients 12 years of age or older with cystic fibrosis and *Phe508del*-gating or *Phe508del*-residual function genotypes. After a 4-week run-in period with ivacaftor or tezacaftor-ivacaftor, patients were randomly assigned to receive elexacaftor-tezacaftor-ivacaftor or active control for 8 weeks. The primary end point was the absolute change in the percentage of predicted forced expiratory volume in 1 second (FEV₁) from baseline through week 8 in the elexacaftor-tezacaftor-ivacaftor group.

Results: After the run-in period, 132 patients received elexacaftor-tezacaftor-ivacaftor and 126 received active control. Elexacaftor-tezacaftor-ivacaftor resulted in a percentage of predicted FEV₁ that was higher by 3.7 percentage points (95% confidence interval [CI], 2.8 to 4.6) relative to baseline and higher by 3.5 percentage points (95% CI, 2.2 to 4.7) relative to active control and a sweat chloride concentration that was lower by 22.3 mmol per liter (95% CI, 20.2 to 24.5) relative to baseline and lower by 23.1 mmol per liter (95% CI, 20.1 to 26.1) relative to active control (P<0.001 for all comparisons). The change from baseline in the Cystic Fibrosis Questionnaire-Revised respiratory domain score (range, 0 to 100, with higher scores indicating better quality of life) with elexacaftor-tezacaftor-ivacaftor was 10.3 points (95% CI, 8.0 to 12.7) and with active control was 1.6 points (95% CI, -0.8 to 4.1). The incidence of adverse events was similar in the two groups; adverse events led to treatment discontinuation in one patient (elevated aminotransferase level) in the elexacaftor-tezacaftor-ivacaftor group and in two patients (anxiety or depression and pulmonary exacerbation) in the active control group.

Conclusions: Elexacaftor-tezacaftor-ivacaftor was efficacious and safe in patients with *Phe508del*-gating or *Phe508del*-residual function genotypes and conferred additional benefit relative to previous CFTR modulators. (Funded by Vertex Pharmaceuticals; VX18-445-104 ClinicalTrials.gov number, [NCT04058353](https://clinicaltrials.gov/ct2/show/study/NCT04058353).)

McKone EF, DiMango EA, Sutharsan S, et al. A phase 3, randomized, double-blind, parallel-group study to evaluate tezacaftor/ivacaftor in people with cystic fibrosis heterozygous for F508del-CFTR and a gating mutation. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* Mar 2021;20(2):234-242. doi:10.1016/j.jcf.2020.11.003

Background: Tezacaftor (TEZ)/ivacaftor (IVA) is an approved CFTR modulator shown to be efficacious and generally safe and well tolerated in people ≥12 years of age with cystic fibrosis (CF) homozygous for the F508del-CFTR mutation or heterozygous for the F508del-CFTR mutation and a residual function mutation. Although previous studies with IVA alone showed clinical benefits in people with CFTR gating mutations, TEZ/IVA has not yet been evaluated in a Phase 3 study of participants heterozygous for F508del-CFTR and a gating mutation (F/gating genotypes). Here, we present results from a randomized, double-blind, IVA-controlled, parallel-group, Phase 3 study assessing the efficacy, safety, and pharmacokinetics (PK) of TEZ/IVA in participants ≥12 years of age with F/gating genotypes.

Methods: Enrolled participants entered a 4-week IVA run-in period to create a stable IVA baseline. Participants were then randomized to receive IVA or TEZ/IVA for 8 weeks in an active comparator treatment period (ACTP). The primary endpoint was absolute change in percent predicted forced expiratory volume in 1 second (ppFEV₁). Key secondary endpoints were relative change in ppFEV₁ and absolute change in CF Questionnaire-Revised respiratory domain score. Secondary endpoints included absolute change in sweat chloride (SwCl) concentration, PK parameters, and safety. All endpoints except PK parameters and safety were assessed from baseline through Week 8.

Results: Sixty-nine participants (92.0%) in the IVA group and 75 participants (98.7%) in the TEZ/IVA group completed treatment. No improvements were seen in efficacy endpoints from baseline at the end of the IVA run-in period through the end of the ACTP in the IVA group. No significant differences in ppFEV₁ or any

key secondary endpoint were observed between the IVA and TEZ/IVA groups. SwCl concentrations decreased more in the TEZ/IVA versus IVA group during the ACP. The safety profile and PK parameters of TEZ/IVA were consistent with those of previous studies in participants ≥ 12 years of age with CF.

Conclusions: This Phase 3 study showed that the dual-combination regimen of TEZ/IVA demonstrated clinical efficacy but did not have significantly greater clinical efficacy than IVA alone in participants ≥ 12 years of age with F/gating genotypes. However, as reported in other studies, TEZ/IVA was generally safe and well tolerated (NCT02412111).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to August 11, 2025>

1	Cystic Fibrosis Transmembrane Conductance Regulator/	11669
2	elxacaftor.mp.	906
3	ivacaftor.mp.	1923
4	lumacaftor.mp.	668
5	tezacaftor.mp.	1024
6	vanzacaftor.mp.	10
7	deutivacaftor.mp.	9
8	CFTR potentiators.mp.	100
9	CFTR correctors.mp.	137
10	cystic fibrosis.mp. or Cystic Fibrosis/	61920
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	12582
12	10 and 11	12482
13	limit 12 to (english language and humans and yr="2020 -Current" and (clinical trial, phase iii or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or "systematic review"))	104
14	from 13 keep 9-12,24,34-37,43-44,52-53,57,65,70,72,75,77,79,81,96-97,99	12

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALYFTREK safely and effectively. See full prescribing information for ALYFTREK.

ALYFTREK (vanzacaftor, tezacaftor, and deuterivacaftor tablets), for oral use

Initial U.S. Approval: 2024

WARNING: DRUG-INDUCED LIVER INJURY AND LIVER FAILURE

See full prescribing information for complete boxed warning.

- Elevated transaminases have been observed in patients treated with ALYFTREK (5.1, 6).
- Cases of serious and potentially fatal drug-induced liver injury and liver failure leading to transplantation and death were reported in patients who were taking ELX/TEZ/IVA, a drug containing the same or similar active ingredients as ALYFTREK (5.1).
- Assess liver function tests (ALT, AST, alkaline phosphatase, bilirubin) in all patients prior to initiating ALYFTREK, every month for first 6 months, every 3 months for next 12 months, then at least annually (2.1, 5.1).
- Interrupt ALYFTREK for significant elevations in LFTs or signs or symptoms of liver injury. Follow patients closely with clinical and laboratory monitoring until abnormalities resolve (5.1).
- Resume ALYFTREK if abnormalities resolve and only if the benefit is expected to outweigh the risk (5.1).
- 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) (2.4, 5.1, 8.7, 12.3).

INDICATIONS AND USAGE

ALYFTREK is a combination of deuterivacaftor, a CFTR potentiator, tezacaftor, and vanzacaftor 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 *CFTR* gene. (1, 12.1)

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. (1, 12.1)

DOSAGE AND ADMINISTRATION

Prior to initiating ALYFTREK obtain liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) in all patients. Monitor liver function tests every month during the first 6 months of treatment, then every 3 months during the next 12 months, then at least annually thereafter. (2.1, 5.1)

Recommended Dosage for Adult and Pediatric Patients Aged 6 Years and Older (with fat-containing food) (2.2)

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/deuterivacaftor 50 mg
	Greater than or equal to 40 kg	Two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deuterivacaftor 125 mg
12 years and older	Any Weight	Two tablets of vanzacaftor 10 mg/tezacaftor 50 mg/deuterivacaftor 125 mg

- Should not be used in patients with severe hepatic impairment. Use not recommended in patients with moderate hepatic impairment unless the benefit outweighs the risk. If used, no dose adjustment is recommended. Liver function tests should be closely monitored. (2.4, 5.1, 6.1, 8.7)
- See full prescribing information for dosage modifications for concomitant use of ALYFTREK with strong or moderate CYP3A inhibitors. (2.3, 5.5, 7.1)

DOSAGE FORMS AND STRENGTHS

Tablets:

- Fixed-dose combination containing vanzacaftor 4 mg, tezacaftor 20 mg, and deuterivacaftor 50 mg. (3)
- Fixed-dose combination containing vanzacaftor 10 mg, tezacaftor 50 mg, and deuterivacaftor 125 mg. (3)

CONTRAINDICATIONS

None. (4)

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 with a drug that contains the same or similar active ingredients as ALYFTREK. Assess liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) in all patients prior to initiating and throughout treatment with ALYFTREK. Interrupt ALYFTREK in the event of significant elevations in liver function tests or signs or symptoms of liver injury. 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). (2.4, 5.1, 8.7)
- Hypersensitivity Reactions:** Hypersensitivity reactions, including anaphylaxis, have been reported in the postmarketing setting for drugs containing elexacaftor, tezacaftor, and/or ivacaftor. If signs or symptoms of serious hypersensitivity reactions develop during ALYFTREK treatment, discontinue ALYFTREK and initiate appropriate therapy. (5.2)
- Patients Who Discontinued or Interrupted Elexacaftor-, Tezacaftor-, or Ivacaftor-Containing Drugs Due to Adverse Reactions:** Consider benefits and risks before using ALYFTREK in patients who discontinued or interrupted elexacaftor-, tezacaftor-, or ivacaftor-containing drugs due to adverse reactions. If ALYFTREK is used, closely monitor for adverse reactions as clinically appropriate. (5.3)
- Reduced Effectiveness in Patients with Concomitant Use with CYP3A Inducers:** Concomitant use with strong and moderate CYP3A inducers decreased vanzacaftor, tezacaftor, and deuterivacaftor exposure, which may reduce ALYFTREK efficacy. Therefore, concomitant use is not recommended. (5.4, 7.1)
- Adverse Reactions with Concomitant Use with CYP3A Inhibitors:** Concomitant use with strong or moderate CYP3A inhibitors increased vanzacaftor, tezacaftor, and deuterivacaftor exposure, which may increase the risk of ALYFTREK associated adverse reactions. Reduce the ALYFTREK dosage with concomitant use. (2.3, 5.5, 7.1)
- Cataracts:** Non-congenital lens opacities/cataracts have been reported in patients with CF aged 18 years or less treated with drugs containing ivacaftor. Baseline and follow up ophthalmological examinations are recommended in pediatric patients treated with ALYFTREK. (5.6, 8.4)

ADVERSE REACTIONS

Most common adverse reactions to ALYFTREK ($\geq 5\%$ of patients and at a frequency higher than ELX/TEZ/IVA by $\geq 1\%$) were cough, nasopharyngitis, upper respiratory tract infection, headache, oropharyngeal pain, influenza, fatigue, increased ALT, rash, increased AST, and sinus congestion. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Vertex Pharmaceuticals Incorporated at 1-877-634-8789 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong or moderate CYP3A inducers:** Concomitant use with ALYFTREK is not recommended. (5.4, 7.1)
- Strong or moderate CYP3A inhibitors:** Reduce ALYFTREK dosage with concomitant use. Avoid food or drink containing grapefruit. (2.3, 5.5, 7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2024

<i>711+3A→G</i> *	<i>F311del</i>	<i>I148T</i>	<i>R75Q</i>	<i>S589N</i>
<i>2789+5G→A</i> *	<i>F311L</i>	<i>I175V</i>	<i>R117C</i> *	<i>S737F</i>
<i>3272-26A→G</i> *	<i>F508C</i>	<i>I807M</i>	<i>R117G</i>	<i>S945L</i> *
<i>3849+10kbC→T</i> *	<i>F508C;S1251N</i> *	<i>I1027T</i>	<i>R117H</i> *	<i>S977F</i> *
<i>A120T</i>	<i>F1052V</i>	<i>I1139V</i>	<i>R117L</i>	<i>S1159F</i>
<i>A234D</i>	<i>F1074L</i>	<i>K1060T</i>	<i>R117P</i>	<i>S1159P</i>
<i>A349V</i>	<i>G178E</i>	<i>L206W</i> *	<i>R170H</i>	<i>S1251N</i> *
<i>A455E</i> *	<i>G178R</i> *	<i>L320V</i>	<i>R347H</i> *	<i>S1255P</i> *
<i>A1067T</i>	<i>G194R</i>	<i>L967S</i>	<i>R347L</i>	<i>T338I</i>
<i>D110E</i>	<i>G314E</i>	<i>L997F</i>	<i>R352Q</i> *	<i>T1053I</i>
<i>D110H</i>	<i>G551D</i> *	<i>L1480P</i>	<i>R553Q</i>	<i>V232D</i>
<i>D192G</i>	<i>G551S</i> *	<i>M152V</i>	<i>R668C</i>	<i>V562I</i>
<i>D579G</i> *	<i>G576A</i>	<i>M952I</i>	<i>R792G</i>	<i>V754M</i>
<i>D924N</i>	<i>G970D</i>	<i>M952T</i>	<i>R933G</i>	<i>V1293G</i>
<i>D1152H</i> *	<i>G1069R</i>	<i>P67L</i> *	<i>R1070Q</i>	<i>W1282R</i>
<i>D1270N</i>	<i>G1244E</i> *	<i>Q237E</i>	<i>R1070W</i> *	<i>Y1014C</i>
<i>E56K</i>	<i>G1249R</i>	<i>Q237H</i>	<i>R1162L</i>	<i>Y1032C</i>
<i>E193K</i>	<i>G1349D</i> *	<i>Q359R</i>	<i>R1283M</i>	
<i>E822K</i>	<i>H939R</i>	<i>Q1291R</i>	<i>S549N</i> *	
<i>E831X</i> *	<i>H1375P</i>	<i>R74W</i>	<i>S549R</i> *	

Table 6: List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to SYMDEKO

<i>546insCTA</i>	<i>E92K</i>	<i>G576A</i>	<i>L346P</i>	<i>R117G</i>	<i>S589N</i>
<i>711+3A→G*</i>	<i>E116K</i>	<i>G576A;R668C†</i>	<i>L967S</i>	<i>R117H</i>	<i>S737F</i>
<i>2789+5G→A*</i>	<i>E193K</i>	<i>G622D</i>	<i>L997F</i>	<i>R117L</i>	<i>S912L</i>
<i>3272-26A→G*</i>	<i>E403D</i>	<i>G970D</i>	<i>L1324P</i>	<i>R117P</i>	<i>S945L*</i>
<i>3849+10kbC→T*</i>	<i>E588V</i>	<i>G1069R</i>	<i>L1335P</i>	<i>R170H</i>	<i>S977F*</i>
<i>A120T</i>	<i>E822K</i>	<i>G1244E</i>	<i>L1480P</i>	<i>R258G</i>	<i>S1159F</i>
<i>A234D</i>	<i>E831X</i>	<i>G1249R</i>	<i>M152V</i>	<i>R334L</i>	<i>S1159P</i>
<i>A349V</i>	<i>F191V</i>	<i>G1349D</i>	<i>M265R</i>	<i>R334Q</i>	<i>S1251N</i>
<i>A455E*</i>	<i>F311del</i>	<i>H939R</i>	<i>M952I</i>	<i>R347H*</i>	<i>S1255P</i>
<i>A554E</i>	<i>F311L</i>	<i>H1054D</i>	<i>M952T</i>	<i>R347L</i>	<i>T338I</i>
<i>A1006E</i>	<i>F508C</i>	<i>H1375P</i>	<i>P5L</i>	<i>R347P</i>	<i>T1036N</i>
<i>A1067T</i>	<i>F508C;S1251N†</i>	<i>I148T</i>	<i>P67L*</i>	<i>R352Q*</i>	<i>T1053I</i>
<i>D110E</i>	<i>F508del^</i>	<i>I175V</i>	<i>P205S</i>	<i>R352W</i>	<i>V201M</i>
<i>D110H*</i>	<i>F575Y</i>	<i>I336K</i>	<i>Q98R</i>	<i>R553Q</i>	<i>V232D</i>
<i>D192G</i>	<i>F1016S</i>	<i>I601F</i>	<i>Q237E</i>	<i>R668C</i>	<i>V562I</i>
<i>D443Y</i>	<i>F1052V</i>	<i>I618T</i>	<i>Q237H</i>	<i>R751L</i>	<i>V754M</i>
<i>D443Y;G576A;R668C†</i>	<i>F1074L</i>	<i>I807M</i>	<i>Q359R</i>	<i>R792G</i>	<i>V1153E</i>
<i>D579G*</i>	<i>F1099L</i>	<i>I980K</i>	<i>Q1291R</i>	<i>R933G</i>	<i>V1240G</i>
<i>D614G</i>	<i>G126D</i>	<i>I1027T</i>	<i>R31L</i>	<i>R1066H</i>	<i>V1293G</i>
<i>D836Y</i>	<i>G178E</i>	<i>I1139V</i>	<i>R74Q</i>	<i>R1070Q</i>	<i>W1282R</i>
<i>D924N</i>	<i>G178R</i>	<i>I1269N</i>	<i>R74W</i>	<i>R1070W*</i>	<i>Y109N</i>
<i>D979V</i>	<i>G194R</i>	<i>I1366N</i>	<i>R74W;D1270N†</i>	<i>R1162L</i>	<i>Y161S</i>
<i>D1152H*</i>	<i>G194V</i>	<i>K1060T</i>	<i>R74W;V201M†</i>	<i>R1283M</i>	<i>Y1014C</i>
<i>D1270N</i>	<i>G314E</i>	<i>L15P</i>	<i>R74W;V201M;D1270N†</i>	<i>R1283S</i>	<i>Y1032C</i>
<i>E56K</i>	<i>G551D</i>	<i>L206W*</i>	<i>R75Q</i>	<i>S549N</i>	
<i>E60K</i>	<i>G551S</i>	<i>L320V</i>	<i>R117C*</i>	<i>S549R</i>	

* Clinical data for these mutations in Clinical Studies [see Clinical Studies (14.1 and 14.2)].

^ A patient must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented in Table 6 to be indicated.

† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

Table 6: List of CFTR Gene Mutations Responsive to TRIKAFTA					
Mutations responsive to TRIKAFTA based on clinical data¹					
<i>2789+5G→A</i>	<i>D1152H¹</i>	<i>L206W¹</i>	<i>R1066H¹</i>	<i>S945L¹</i>	
<i>3272-26A→G</i>	<i>F508del¹</i>	<i>L997F¹</i>	<i>R117C¹</i>	<i>T338I¹</i>	
<i>3849+10kbC→T</i>	<i>G85E¹</i>	<i>M1101K¹</i>	<i>R347H¹</i>	<i>V232D¹</i>	
<i>A455E¹</i>	<i>L1077P¹</i>	<i>P5L¹</i>	<i>R347P¹</i>		
Mutations responsive to TRIKAFTA based on in vitro data¹					
<i>N1303K</i>	<i>F200I</i>	<i>I1139V</i>	<i>P574H</i>	<i>S1045Y</i>	
<i>1507 1515del9</i>	<i>F311del</i>	<i>I125T</i>	<i>P67L</i>	<i>S108F</i>	
<i>2183A→G</i>	<i>F311L</i>	<i>I1269N</i>	<i>P750L</i>	<i>S1118F</i>	
<i>3141del9</i>	<i>F508C</i>	<i>I1366N</i>	<i>Q1291R</i>	<i>S1159F</i>	
<i>546insCTA</i>	<i>F508C;S1251N</i>	<i>I148N</i>	<i>Q1313K</i>	<i>S1159P</i>	
<i>A1006E</i>	<i>F575Y</i>	<i>I148T</i>	<i>Q237E</i>	<i>S1235R</i>	
<i>A1067P</i>	<i>F587I</i>	<i>I175V</i>	<i>Q237H</i>	<i>S1251N</i>	
<i>A1067T</i>	<i>G1047R</i>	<i>I331N</i>	<i>Q359R</i>	<i>S1255P</i>	
<i>A107G</i>	<i>G1061R</i>	<i>I336K</i>	<i>Q372H</i>	<i>S13F</i>	

A120T	G1069R	I502T	Q493R	S341P
A234D	G1123R	I506L	Q552P	S364P
A309D	G1244E	I556V	Q98R	S492F
A349V	G1247R	I601F	R1048G	S549I
A46D	G1249R	I618T	R1070Q	S549N
A554E	G126D	I807M	R1070W	S549R
A62P	G1349D	I980K	R1162L	S589N
C491R	G178E	K1060T	R117C;G576A;R668C	S737F
D110E	G178R	K162E	R117G	S912L
D110H	G194R	K464E	R117H	S977F
D1270N	G194V	L1011S	R117L	T1036N
D1445N	G27E	L1324P	R117P	T1053I
D192G	G27R	L1335P	R1283M	T1086I
D443Y	G314E	L137P	R1283S	T1246I
D443Y;G576A;R668C	G424S	L1480P	R170H	T1299I
D565G	G463V	L15P	R258G	T351I
D579G	G480C	L165S	R297Q	V1153E
D614G	G480S	L320V	R31C	V1240G
D836Y	G551A	L333F	R31L	V1293G
D924N	G551D	L333H	R334L	V201M
D979V	G551S	L346P	R334Q	V392G
D993Y	G576A	L441P	R347L	V456A
E116K	G576A;R668C	L453S	R352Q	V456F
E116Q	G622D	L619S	R352W	V562I
E193K	G628R	L967S	R516S	V603F
E292K	G970D	M1137V	R553Q	V754M
E403D	G970S	M150K	R555G	W1098C
E474K	H1054D	M152V	R668C	W1282R
E56K	H1085P	M265R	R709Q	W361R
E588V	H1085R	M952I	R74Q	Y1014C
E60K	H1375P	M952T	R74W	Y1032C
E822K	H139R	N1088D	R74W;D1270N	Y109N
E92K	H199Y	N1303I	R74W;V201M	Y161D
F1016S	H620P	N186K	R74W;V201M;D1270N	Y161S
F1052V	H620Q	N187K	R751L	Y301C
F1074L	H939R	N418S	R75L	Y563N
F1099L	H939R;H949L	P140S	R75Q	
F1107L	I1027T	P205S	R792G	
F191V	I105N	P499A	R933G	

Mutations responsive to TRIKAFTA based on extrapolation from Trial 5[§]

4005+2T→C	2789+2insA	3849+40A→G	5T;TG13	
1341G→A	296+28A→G	3849+4A→G	621+3A→G	
1898+3A→G	3041-15T→G	3850-3T→G	711+3A→G	
2752-26A→G	3600G→A	5T;TG12	E831X	

* Clinical data obtained from Trials 1, 2, and 5.

† This mutation is also predicted to be responsive by FRT assay.

‡ The N1303K mutation is predicted to be responsive by HBE assay. All other mutations predicted to be responsive with in vitro data are supported by FRT assay.

§ Efficacy is extrapolated from Trial 5 to non-canonical splice mutations because clinical trials in all mutations of this subgroup are infeasible and these mutations are not amenable to interrogation by FRT system.

Table 5: List of CFTR Gene Mutations Responsive to ALYFTREK

Based on Clinical Data [†]						
A455E	G551D	L1077P [†]	R352Q	S549N	V754M	
D1152H	G85E [†]	L206W	R75Q	S549R	W1098C [‡]	
F508del [†]	H1054D	M1101K [†]	S1159F	S945L	W1282R	
G1244E	I336K	R1066H	S1251N	V562I	Y563N [†]	
Based on in vitro Data [‡]						
I507 I515del ⁹	E116Q	G424S	I556V	P140S	R334L	T1053I
2183.A→G	E193K	G463V	I601F	P205S	R334Q	T1086I
3141del ⁹	E292K	G480C	I618T	P499.A	R347H	T1246I
3195del ⁶	E403D	G480S	I807M	P5L	R347L	T1299I
3199del ⁶	E474K	G551.A	I980K	P574H	R347P	T338I
S40ins:CT.A	E56K	G551S	K1060T	P67L	R352W	T351I
A1006E	E588V	G576.A	K162E	P750L	R516G	T604I
A1067P	E60K	G576.A;R668C [‡]	K464E	P99L	R516S	V1153E
A1067T	E822K	G622D	L1011S	Q1100P	R553Q	V1240G
A107G	E92K	G628R	L102R	Q1291R	R555G	V1293G
A120T	F1016S	G91R	L1065P	Q1313K	R560S	V201M
A234D	F1052V	G970D	L1324P	Q237E	R560T	V232D
A309D	F1074L	G970S	L1335P	Q237H	R668C	V392G
A349V	F1099L	H1085P	L137P	Q359R	R709Q	V456.A
A46D	F1107L	H1085R	L1480P	Q372H	R74Q	V456F
A554E	F191V	H1375P	L15P	Q452P	R74W	V520F
A559T	F200I	H139R	L165S	Q493R	R74W;D1270N [‡]	V603F
A559V	F311del	H199R	L320V	Q552P	R74W;V201M [‡]	W361R
A561E	F311L	H199Y	L333F	Q98R	R74W;V201M;D1270N [‡]	Y1014C
A613T	F508C	H609R	L333H	R1048G	R75L	Y1032C
A62P	F508C;S1251N [‡]	H620P	L346P	R1066C	R751L	Y109N
A72D	F575Y	H620Q	L441P	R1066L	R792G	Y161D
C491R	F587I	H939R	L453S	R1066M	R933G	Y161S
D110E	G1047R	H939R;H949L	L619S	R1070Q	S1045Y	Y301C
D110H	G1061R	I1027T	L967S	R1070W	S108F	Y569C
D1270N	G1069R	I105N	L997F	R1162L	S1118F	Y913C
D1445N	G1123R	I1139V	M1101R	R117C	S1159P	
D192G	G1247R	I1234Vdel6aa	M1137V	R117C;G576.A;R668C	S1235R	
D443Y	G1249R	I125T	M150K	R117G	S1255P	
D443Y;G576.A;R668C [‡]	G126D	I1269N	M152V	R117H	S13F	
D513G	G1349D	I331N	M265R	R117L	S341P	
D565G	G149R	I1366N	M952I	R117P	S364P	
D579G	G178E	I1398S	M952T	R1283M	S492F	
D614G	G178R	I148N	N1088D	R1283S	S549I	
D836Y	G194R	I148T	N1303I	R170H	S589N	
D924N	G194V	I175V	N1303K [‡]	R258G	S737F	
D979V	G27E	I502T	N186K	R297Q	S912L	
D993Y	G27R	I506L	N187K	R31C	S977F	

<i>E116K</i>	<i>G314E</i>	<i>I506T</i>	<i>N418S</i>	<i>R31L</i>	<i>T1036N</i>	
Based on Extrapolation[†]						
<i>1341G→A</i>	<i>2789+2ins.A</i>	<i>3041-15T→G</i>	<i>3849+10kbC→T</i>	<i>3850-3T→G</i>	<i>5T;TG13</i>	<i>711+3.A→G</i>
<i>1898+3.A→G</i>	<i>2789+5G→A</i>	<i>3272-26.A→G</i>	<i>3849+4.A→G</i>	<i>4005+2T→C</i>	<i>621+3.A→G</i>	<i>E831X</i>
<i>2752-26.A→G</i>	<i>296+28.A→G</i>	<i>3600G→A</i>	<i>3849+40.A→G</i>	<i>5T;TG12</i>		
[*] Clinical data is obtained from Trials 1 and 2. [†] This mutation is also predicted to be responsive by FRT assay with ALYFTREK. [‡] The <i>N1303K</i> mutation is predicted to be responsive only by HBE assay. All other mutations predicted to be responsive with in vitro data are supported by FRT assay. [§] Complex/compound mutations where a single allele of the <i>CFTR</i> gene has multiple mutations; these exist independent of the presence of mutations on the other allele. [¶] Efficacy is extrapolated to certain non-canonical splice mutations because clinical trials in all mutations in this subgroup are infeasible and these mutations are not amenable to interrogation by FRT system.						

Cystic Fibrosis Modulators, Oral

Goals:

- To ensure appropriate drug use and limit to patient populations in which they have demonstrated to be effective and safe.
- To monitor for clinical response for appropriate continuation of therapy.

Length of Authorization:

- 6 months

Requires PA:

- Ivacaftor (Kalydeco®)
- Lumacaftor/Ivacaftor (Orkambi®)
- Tezacaftor/Ivacaftor (Symdeko®)
- Elexacaftor/Tezacaftor/Ivacaftor (Trikafta™)
- Vanzacaftor/Tezacaftor/Deutivacaftor (Alyftrek™)

Preferred Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: Approved and Funded Indications for Oral Cystic Fibrosis Modulators

Drug Name	FDA approved CFTR mutation	Age
Ivacaftor (Kalydeco)	E56K, G178R, S549R K1060T, G1244E, P67L, E193K, G551D, A1067T, S1251N R74W, L206W, G551S, G1069R, S1255P, D110E, R347H, D579G, R1070Q, D1270N, D110H, R352Q, S945L, R1070W G1349D, R117C, A455E, S977F, F1074L, R117H, S549N, F1052V, D1152H 3849 + 10kbC -T, 2789 +5G>A, 3272-26A-G, 711+3A-G, E831X, R117H or a mutation in the CFTR gene that is responsive based on in vitro data. See drug labeling for a comprehensive list of approved mutations: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=203188	4 months to < 6 months AND ≥ 5 kg ≥ 6 months

Lumacaftor/ivacaftor (Orkambi)	Homozygous Phe508del	≥ 1 year
Tezacaftor/ivacaftor (Symdeko)	Homozygous Phe508del, A455E, A1067T, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R74W, R1070W, R117C, R347H, R352Q, S945L, S977F, 711+3A→G, 2789+5G→A, 3272-26A→G, 3849+10kbC→T or a mutation in the CFTR gene that is responsive based on in vitro data. See drug labeling for a comprehensive list of approved mutations: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=210491	≥ 6 years
Elexacaftor/tezacaftor/ivacaftor (Trikafta)	At least one Phe508del mutation (homozygous or heterozygous) or a mutation in the CFTR gene that is responsive based on in vitro data. See drug labeling for a comprehensive list of mutations: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=212273	≥ 2 years
Vanzacaftor/Tezacaftor/Deutivacaftor (Alyftrek)	At least one Phe508del mutation or another responsive mutation in the CFTR gene. See drug labeling for a comprehensive list of mutations: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=218730	≥ 6 years

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program (patient already on ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, vancacaftor/tezacaftor/duetivacftor or elexacaftor/tezacaftor/ivacaftor)?	Yes: Go to Renewal Criteria	No: Go to #2
2. Does the patient have a diagnosis of Cystic Fibrosis?	Yes: Record ICD10 code. Go to #3	No: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Is the request from a practitioner at an accredited Cystic Fibrosis Center or a pulmonologist?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is the request for an FDA approved age and CFTR gene mutation as defined in Table 1?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use.
5. How many exacerbations and/or hospitalizations in the past 12 months has the patient had?	Prescriber must provide documentation before approval. Document baseline value. Go to #6	
6. Is the request for ivacaftor?	Yes: Go to #7	No: Go to #8
7. Does the patient have a documented R117H mutation in the CFTR gene detected by a CF mutation test?	Yes: Pass to RPh. Refer request to Medical Director for manual review and assessment of clinical severity of disease for approval.	No: Go to #8 If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).

Approval Criteria		
8. Is the patient on concomitant therapy with a strong CYP3A4 inducer (see Table 1)?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #9
9. What are the baseline liver function (AST/ALT) and bilirubin levels (within previous 3 months)?	Document labs. Go to #10 If unknown, these labs need to be collected prior to approval.	
10. Is medication dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	Yes: Approve for 6 months. If approved, a referral will be made to case management by the Oregon Health Authority.	No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?	Yes: Go to #2	No: Pass to RPh; Deny (medical appropriateness)

Renewal Criteria

<p>2. Does the patient have documented response to therapy as defined as below :</p> <p>For patients age ≥ 6 years:</p> <ul style="list-style-type: none"> • An improvement or lack of decline in lung function as measured by the FEV1 when the patient is clinically stable; OR • A reduction in the incidence of pulmonary exacerbations; OR • A significant improvement in BMI by 10% from baseline? <p>For patients age 2-5 years (cannot complete lung function tests)</p> <ul style="list-style-type: none"> • Significant improvement in BMI by 10% from baseline; OR • Improvement in exacerbation frequency or severity 	<p>Yes: Go to #3</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>
<p>3. Have liver function tests been appropriately monitored? What are the most recent liver function tests (AST, ALT, and bilirubin)?</p> <p>Note: Monitoring LFTs is recommended every every month for the first 6 months, then every 3 months for the next 12 months, then at least annually.</p>	<p>Document. Go to #4</p> <p>Note: Therapy should be interrupted in patients with AST or ALT $>5x$ the upper limit of normal (ULN), or ALT or AST $>3x$ ULN with bilirubin $>2x$ ULN.</p>	
<p>4. Is the CFTR modulator dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?</p>	<p>Yes: Approve for additional 12 months</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>

Dosage and Administration:

Ivacaftor:

- Adults and pediatrics age ≥ 6 years: 150 mg orally every 12 hours with fat-containing foods
- Children age 6 months to < 6 years:
 - 5 kg to < 7 kg: 25 mg packet every 12 hours
 - 7 kg to < 14 kg: 50 mg packet every 12 hours
 - ≥ 14 kg: 75 mg packet every 12 hours
- Hepatic Impairment
 - Moderate Impairment (Child-Pugh class B):
 - Age ≥ 6 years: one 150 mg tablet once daily
 - Age 6 months to < 6 years
 - with body weight < 14 kg: 50 mg packet once daily
 - with body weight ≥ 14 kg : 75 mg packet of granules once daily
 - Severe impairment (Child-Pugh class C): Use with caution at a dose of 1 tablet or 1 packet of oral granules once daily or less frequently. For infants, children and adolescents: administer usual dose once daily or less frequently. Use with caution.
- Dose adjustment with concomitant medications:

Table 1. Examples of CYP3A4 inhibitors and inducers.

Drug co-administered with IVA	Co-administered drug category	Recommended dosage adjustment for IVA
Ketoconazole Itraconazole Posaconazole Voriconazole Clarithromycin Telithromycin	CYP3A4 strong inhibitors	Reduce IVA dose to 1 tablet or 1 packet of oral granules twice weekly (one-seventh of normal initial dose)
Fluconazole Erythromycin Clofazimine	CYP3A4 moderate inhibitors	Reduce IVA dose to 1 tablet or 1 packet of oral granules once daily (half of normal dose)

Rifampin Rifabutin Phenobarbital Phenytoin Carbamazepine St. John's wort	CYP3A4 strong inducers	Concurrent use is NOT recommended
Grapefruit Juice	CYP3A4 moderate inhibitors	

Lumacaftor/ivacaftor

- Adults and pediatrics age ≥ 12 years: 2 tablets (LUM 200 mg/IVA 125 mg) every 12 hours
- Pediatric patients age 6 through 11 years: 2 tablets (LUM 100mg/IVA 125 mg) every 12 hours
- Children age 2 to <6 years:
 - < 14 kg: 1 packet (LUM 100mg/IVA125mg) every 12 hours
 - ≥ 14 kg: 1 packet (LUM 150mg/IVA 188mg) every 12 hours
- Hepatic impairment
 - Moderate impairment (Child-Pugh class B):
 - Age ≥ 6 years: 2 tablets in the morning and 1 tablet in the evening
 - Age 2 to <6 years: 1 packet in the morning and 1 packet every other day in the evening
 - Severe impairment (Child-Pugh class C): Use with caution after weighing the risks and benefits of treatment.
 - Age ≥ 6 years: 1 tablet twice daily, or less
 - Age 2 to <6 years: 1 packet once daily, or less
- Dose adjustment with concomitant medications:
 - When initiating therapy in patients taking strong CYP3A inhibitors (see table above), reduce dose to 1 tablet daily for the first week of treatment. Following this period, continue with the recommended daily dose.

Tezacaftor/ivacaftor:

- Adults and pediatrics age ≥ 6 years weighing ≥ 30 kg : 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning and IVA 150 mg in the evening
- Pediatrics age ≥ 6 years weighing < 30 kg: TEZ 50mg/IVA 75 mg in the morning and IVA 75 mg in the evening
- Hepatic impairment
 - Moderate impairment (Child-Pugh class B):
 - 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning. The evening IVA dose should not be administered.
 - Severe impairment (Child-Pugh class C):
 - 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning (or less frequently). The evening IVA dose should not be administered.
- Dose adjustment with concomitant medications:

- When initiating therapy in patients taking moderate CYP3A inhibitors (see table above), reduce dose to:
 - On day 1, TEZ 100/IVA 150 once daily in the morning, and on day 2, IVA 150 mg once daily in the morning; continue this dosing schedule.
- When initiating therapy in patients taking strong CYP3A4 inhibitors (See table above), reduce dose to:
 - TEZ 100 mg/IVA 150 mg twice a week, administered 3 to 4 days apart. The evening dose of IVA 150 mg should not be administered.

Elexacaftor/tezacaftor/ivacaftor:

- Adults and pediatrics age ≥12 years and ≥ 6 years and weight ≥ 30 kg: 2 tablets (ELX 100mg/TEZ 50 mg/IVA 75 mg) in the morning and IVA 150 mg in the evening
- Pediatrics 6 to < 12 years
 - Weight < 30 kg: 2 tablets (ELX 50 mg/TEZ mg/IVA 37.5 mg) in the morning and one IVA 75 mg in the evening
- Pediatrics 2 to < 6 years:
 - Weight < 14 kg: 1 oral granule packet (ELX 80 mg/ TEZ 40 mg/ IVA 60 mg) in the morning and one IVA 59.5 mg in the evening
 - Weight ≥ 14 kg: 1 oral granule packet (ELX 100 mg/ TEZ 50 mg/ IVA 75 mg) in the morning and one IVA 75 mg in the evening
- Hepatic impairment
 - Moderate impairment (Child-Pugh class B): Use only if the benefits outweigh the risks.
 - 2 tablet (ELX 100 mg/TEZ 50 mg/IVA 75 mg) in the morning. The evening IVA dose should not be administered.
 - Severe impairment (Child-Pugh class C): Use not recommended
- Dose adjustment with concomitant medications:
 - Dosage adjustment for concomitant therapy with moderate CYP3A inhibitors (see table above):
 - 2 tablets (ELX 100 mg/ TEZ 50 mg/IVA 75 mg once daily in the morning, alternating with one IVA 150 mg tablet in the morning every other day.
 - Dosage adjustment for concomitant therapy with strong CYP3A4 inhibitors (See table above), reduce dose to:
 - 2 tablets (ELX 100 mg/TEZ 50 mg/IVA 75 mg twice a week, administered 3 to 4 days apart. The evening dose of IVA 150 mg should not be administered.

Vanzacaftor/tezacaftor/deutivacaftor

- Adults and children ≥ 12 years: 2 tablets (VNZ 10 mg/TEZ 50 mg/D-IVA 250 mg) once daily
- Children 6 to < 12 years:
 - Weight < 40 kg: 3 tablets (VNZ 4 mg/TEZ 20 mg/ D-IVA 50 mg) once daily
 - Weight ≥ 40 kg: 2 tablets (VNZ 10 mg/TEZ 50 mg/D-IVA 250 mg) once daily

Implementation: 1/1/26; 7/1/21; 7/1/20; 11/1/19; 11/1/2018; 1/1/16; 8/25/15; 8/12