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

Date of Review: April 2020

Date of Last Review: September 2019 **(PA update)**
Dates of Literature Search: 08/01/2018 – 01/31/2020
Brand Name (Manufacturer): Trikafta™ (Vertex)
Dossier Received: Yes

Generic Name: elexacaftor/ivacaftor/tezacaftor

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 elexacaftor/ivacaftor/tezacaftor (ELX/TEZ/IVA).

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 insufficient evidence that the oral CF transmembrane conductance regulator (CFTR) modulators (potentiators and correctors), improve survival and overall quality of life.[1,2]
- 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.[1] 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.[2] There is also moderate quality evidence of a decrease in pulmonary exacerbations for both LUM/IVA hazard ratio (HR) 0.70 (95% CI 0.57 to 0.87) and TEZ/IVA (HR 0.64; 95% CI 0.46 to 0.89) compared to placebo.[2]

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- There is moderate strength evidence that IVA alone provides no benefit for respiratory function or quality of life in those with the F508del mutation and no respiratory benefit in those with R177H rotation.[1]
- 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).[3] 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.[3]
- 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).[4] 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.

Recommendations:
- Maintain ELX/TEZ/IVA as non-preferred and add to clinical prior authorization criteria (**Appendix 5**).

Summary of Prior Reviews and Current Policy
- There is low quality evidence that TEZ/IVA modestly improves lung function, decreases pulmonary exacerbations and improves respiratory domain quality of life in those with CF homozygous for the F508del mutation
- There is insufficient evidence that TEZ/IVA has a significant effect on clinical outcomes for the treatment of CF in those heterozygous for the F508del mutation and a second allele predicted to have residual function.
- There is moderate quality evidence that IVA is effective in patients with the G115D mutation. There is insufficient evidence that IVA monotherapy has a clinically relevant impact on other mutations.
- There is insufficient evidence that lumacaftor/ivacaftor (LUM/IVA) has a significant effect on clinically important outcomes for the treatment of CF in those homozygous for the F508del mutation on the CFTR gene. It was associated with only an absolute 2.8% improvement in FEV1 (estimated by averaging the absolute change at weeks 16 and 24) and a nominal decrease in pulmonary exacerbations compared to placebo.
- There is insufficient evidence that LUM/IVA improves lung function in children ages 6 to 11 years old with CF homozygous for the F508del mutation. Approval was based on a phase 3 study evaluating nonclinical outcomes.
- LUM/IVA has not demonstrated a significant effect on FEV1 in patients who are heterozygous for the F508del mutation and therapy should not be used in this patient population.
- Evidence limitations:
    - Evidence remains insufficient to compare the efficacy/effectiveness or safety of CF modulators against standard of care including dornase alfa and hypertonic saline.
    - Evidence remains insufficient to determine the effects of oral CF modulators on long term disease progression or to know if TEZ/IVA is effective in patients with very severe CF (ppFEV1 <40%) or very mild CF (ppFEV1 >90%).
    - Evidence remains insufficient to determine appropriate criteria for discontinuing oral CF modulators for lack of effectiveness.

- There is significant involvement from the manufacturer in all clinical trials of IVA, LUM/IVA and TEZ/IVA including but not limited to: funding, study design, data collection analysis and interpretation as well as writing and publication of the manuscript.

Background:

Cystic Fibrosis (CF) is a genetic disease that can affect multiple organs, of which progressive lung disease is responsible for approximately 85% of mortality observed in this population.[5] Most available treatments for CF focus 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.[6] CF is caused by mutations in the CFTR gene, found on the surface of cells in a variety of tissues where it functions as a regulator of the chloride ion channel.[7] CFTR mutations are often categorized according to their functional impact on CFTR protein synthesis or function (**Table 1**). Over 1900 mutations have been identified in the CFTR gene, with different protein defects resulting from the mutation.[8] 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 to open channels 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. [8] 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.[9] 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, and carries the most severe prognosis.[10] 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 that generally progresses more slowly than more common forms.[11]

Table 1: CFTR mutation categories[12]

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

Clinically meaningful outcomes of CF treatment include mortality, frequency of pulmonary exacerbations, quality of life and respiratory symptoms. Forced expiratory volume in one second (FEV_1) is a commonly used surrogate outcome in clinical trials. A minimal clinically important difference for FEV_1 has not been defined or agreed upon because of the heterogeneous nature of the condition.[13] According to National Institute of Clinical Excellence (NICE), an absolute change in $ppFEV_1$ of 5% or more would be considered clinically important.[13] Changing the FEV_1 rate of decline would be the most meaningful effect, but would require a long study duration. In CF patients, FEV_1 decreases on average by 1-3% per year but varies based on age and baseline lung function.[14] In CF patients with moderate to severe lung disease, inhaled tobramycin and dornase alfa have shown improvement in FEV_1 ranging from 7.8%-12% with inhaled tobramycin and 5.8%-7.3% with dornase alfa.[15] There is also fair evidence to suggest that macrolide antibiotics provide benefit for all levels of disease with improvements in FEV_1 from 3.6%-6.2%.[15] 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.[16] 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 poorer lung function, and increased morbidity and mortality.[16] 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.[15] 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.[8] Sweat chloride has been used as a biomarker for evaluation of change in CFTR activity in clinical trials of IVA.[17] 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 FEV_1. [15] 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.

Ivacaftor (IVA) (Kalydeco®), Tezacaftor/Ivacaftor (TEZ/IVA) (Symdeko®) and lumacaftor/ivacaftor (LUM/IVA) (Orkambi®) are FDA approved oral agents intended to enhance mutant CFTR protein function (**Table 2**).[17] IVA is a CFTR potentiator indicated for the management of CF in patients in patients at least 2 years of age who have one of 38 CFTR mutations (**Table 2**)*.*[18] The most common gating mutations, G551D and R117H, represent approximately 7% of the U.S. CF population.[17] In trials of patients with the G115D mutation, IVA increased FEV_1 by an absolute value of 10.6% compared to placebo within 2 weeks of treatment; a 26% absolute decrease in respiratory exacerbations, a reduction in sweat chloride values by 50-60 mmol/L, and a weight gain of 2.7 kg was also found.[19] IVA is proposed to treat the underlying cause of CF by influencing the basic gene defect which can normalize airway surface liquid and help re-establish mucociliary clearance.[20,21] IVA is designed to increase the time that activated CFTR channels at the cell surface remain open.[20,21]

LUM/IVA is a combination drug that contains the molecular entity LUM which is classified as a CFTR corrector in combination with IVA. The exact mechanism of LUM is unknown, but it may promote more functional folding of the defective F508del CFTR protein, allowing it to get to the cell surface. Previous studies of IVA did not demonstrate a clinical improvement in lung function in patients with an F508del mutation.[6] However, the combination was approved after phase 3 trials demonstrated its efficacy for the management of CF in patients 12 years of age and older who were homozygous for the F508del mutation in the CFTR gene.[22] Phase 2 trials demonstrated lack of improvement in patients heterozygous for the F508del CFTR mutation.[23] It is currently FDA-approved for those age 12 years and older who are homozygous for the F508del mutation in the CFTR gene.[24] This patient group includes approximately 34% of the U.S. CF population.[17] Studies of LUM/IVA did not demonstrate clinically significant results on meaningful outcomes. It was associated with only an absolute 2.8% improvement in FEV_1 (estimated by averaging the absolute change at weeks 16 and 24) and a nominal decrease in pulmonary exacerbations compared to placebo (RR 0.61; 95% CI 0.49 to 0.76). However, this outcome was actually reported as the number of events per 48 weeks which is unreliable since the trial duration was 24 weeks. There is insufficient evidence to assume that a reduction in pulmonary exacerbations is maintained for patients who remain on treatment. It remains unclear if the combination provides more benefit than IVA alone which was found to be deleterious in F508del homozygous adults in previous trials.

TEZ is another CFTR corrector designed to improve the cellular processing and trafficking of normal and mutated CFTR protein to increase the amount of functional CFTR at the cell surface. It has been studied in combination with IVA in two separate phase 3, randomized, double-blind trials in patients 12 years of age or older who were either heterozygous for the F508del mutation with a residual-function CFTR mutation or those homozygous for F508del.[11,25] It had a modest benefit on ppFEV1 in those homozygous for F508del (3.4% absolute change from baseline) and a clinically insignificant improvement in absolute change from baseline in $ppFEV_1$ (mean difference 2.1%; 95% CI 1.2% to 2.9%) with TEZ/IVA compared to IVA monotherapy in patients heterozygous for the F508del mutation.

Elexacaftor (ELX) is also a CFTR corrector.It binds to a different site on the CFTR protein than other current therapies and is theorized to have an additive effect with TEZ in facilitation of cellular processing and trafficking of the F508del-CFTR to increase the amount of protein delivered to the cell surface.

Table 2: CFTR Modulators: Summary of Studied Mutations

Generic Name (Brand)	FDA Approved Indication (in cystic fibrosis)	Specific Mutations Included
Ivacaftor[18] (Kalydeco®)	≥ 6 months with an ivacaftor-responsive gene mutation	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
Lumacaftor/ivacaftor[24] (Orkambi®)	≥ 2 years Homozygous for Phe508del	Homozygous Phe508del
Tezacaftor/ivacaftor[11,25] (Symdeko®)	≥ 6 years who are homozygous for the F5098del mutation OR who have another tezacaftor/ivacaftor-responsive CFTR mutation	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
Elexacaftor/tezacaftor/ivacaftor[26] (Trikafta®)	≥ 12 years who have at least one F508del mutation	See **Appendix 4**

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 2**, 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, and the Canadian Agency for Drugs and Technologies in Health (CADTH) 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:

1. A systematic review of RCTs from the Cochrane Collaboration was done to evaluate the effects of CFTR potentiators (IVA) on clinically important outcomes in children and adults with CF.[1] Trials evaluating IVA in combination with CFTR correctors (TEZ and LUM) were not included in this analysis, which limits the applicability of the results. Overall, 5 RCTs were included in the analysis (n=447). All of the trials were parallel design and all of them were funded by Vertex Pharmaceuticals. Three trials included subjects with the G551D mutation, one with CF individuals homozygous for the F508del mutation, and one included those with the R117H mutation.[1] All of the included trials had a high risk of reporting bias due to missing data for various tertiary outcomes and/or no protocols being available. Additionally, all of the trials had unclear risk of performance bias due to insufficient information to assess appropriate blinding. Lastly, 3 trials had high risk of attrition bias since participant data was excluded from the analysis. As a result, the quality of the evidence was moderate to low.

For any of the mutations studied, there was insufficient evidence to evaluate the effects of IVA on survival, as none of the RCTs reported survival data or deaths. There was also insufficient evidence on total quality of life.[1] For subjects homozygous for the F508del mutation, there is moderate quality evidence of no significant difference in the respiratory domain of quality of life (CFQ-R) between IVA and placebo and no statistically significant difference ppFEV1 at 16 weeks between IVA and placebo (mean difference 2.4%; 95% CI -0.95 to 5.75).[1] From the study in the R117H mutation, there was moderate strength evidence of a significant improvement in CFQ-R respiratory domain score and no significant difference in ppFEV1 change from baseline. The 3 G551D trials provided moderate strength evidence of a statistically significant improvement in change in ppFEV1 from baseline. However, the data was unable to be combined due to differences in the trials. In the two adult trials with G551D, moderate strength evidence suggests a significant higher CFQ-R scores with IVA compared to placebo. However, there was no significant difference in the pediatric trial. There is low strength evidence in all genotypes of no difference in adverse events resulting in treatment discontinuation. [1]

Overall, there was no benefit on respiratory function or quality of life with IVA in people with the F508del mutation and no respiratory benefit seen in people with R177H. There was a statistically significant improvement in lung function in children and adults with the G115D rotation. There is insufficient evidence in all genotypes on overall survival and total quality of life.

2. Another Cochrane Collaboration systematic review evaluated the effects of CFTR correctors approved at the time (LUM and TEZ) in children and adults with Class II CFTR mutations (most commonly F508del).[2] RCTs comparing a CFTR corrector to placebo or another intervention were included, as well as studies when CFTR correctors are administered with the potentiator IVA. A total of 13 trials (n=2215) were included in the qualitative synthesis and 10 were included in the meta-analysis. [2] Twelve RCTs recruited individuals homozygous for F508del, one RCT recruited participants with one F508del mutation and a second mutation with residual function. Five studies evaluated LUM/IVA and 2 studies evaluated TEZ/IVA. Six trials had high risk of selective reporting bias, and 7 trials had unclear risk of selection bias due to unclear sequence generation and allocation concealment. There was insufficient evidence on any outcomes with monotherapy with a CFTR corrector. [2]

   Focusing on the FDA approved combination products (TEZ/IVA and LUM/IVA), there was insufficient evidence on survival as this outcome was not reported in any of the trials. There was high quality evidence of a significant but small improvement in respiratory domain quality of life score (CVQ-R) with LUM/IVA compared to placebo (mean difference 2.62 points; 95% CI 0.64 to 4.59) and moderate quality evidence of an improvement with TEZ/IVA compared to placebo (mean difference 5 points; 95% CI 3.2 to 7.0). [2] There was high quality evidence of an improvement in lung function, as measured by ppFEV1 change from baseline, with LUM/IVA compared to placebo (mean difference 5.21%; 95% CI 3.61 to 6.80).[2] There was moderate quality evidence of an improvement with TEZ/IVA of 6.8% (95% CI 5.3 to 8.3) compared to placebo. There is also moderate quality evidence of a decrease in pulmonary exacerbations for both LUM/IVA (HR 0.70; 95% CI 0.57 to 0.87) and TEZ/IVA (HR 0.64; 95% CI 0.46 to 0.89) compared to placebo. [2]

New Guidelines:
None

New Formulations or Indications:
Additional indications expanding approved age and mutations have been included in prior PA updates. No new formulations or indications have been approved since the last PA criteria update (September 2019).

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New FDA Safety Alerts:
None

Randomized Controlled Trials:
Four citations were manually reviewed from the initial literature search. After further review, 2 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 2 trials are included in the new drug evaluation and summarized in the evidence table (Table 5).

NEW DRUG EVALUATION: elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)

See **Appendix 3** 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:
ELX/TEZ/IVA was FDA approved based on two, phase 3 RCTs in two different CFTR mutation populations.[3,4] The primary outcome in both trials was the absolute change from baseline in ppFEV1 at week 4. Secondary outcomes included the CFQ-R respiratory domain, body mass index (BMI), sweat chloride, and number of pulmonary exacerbations. The trial by Middleton et al. evaluated the efficacy of ELX/TEZ/IVA in CF patients who are heterozygous for the F508del mutation and a second minimal function mutation over 24 weeks.[3] A minimal function mutation makes either no CFTR protein (class I mutation) or for which in vitro data suggest the CFTR protein is not responsive to other CFTR therapies. Previous trials have not shown LUM/IVA or TEZ/IVA to be effective in this population.[12] Minimal function mutations detectable by an FDA assay are included in **Appendix 4**. Pulmonary exacerbations were defined as new or change in antibiotic therapy due to presence of at least 4 of the following symptoms: change in sputum, new hemoptysis, cough, dyspnea, malaise, fever, anorexia, sinus pain, sinus discharge, decrease in pulmonary function by 10%, or radiographic changes.

Overall, there was a statistically significant improvement in ppFEV1 at week 4 compared to placebo with a LS mean treatment difference of 13.8% (95% CI 12.1 to 15.4; $p<0.0001$).[3] This was maintained through week 24 with LS mean treatment difference of 14.3% (95% CI 12.7 to 15.8). Treatment with ELX/TEZ/IVA also resulted in a significant reduction in pulmonary exacerbations through week 24 with 41 total exacerbations in the ELX/TEZ/IVA arm and 113 in the placebo arm (rate ratio 0.37; 95 % CI 0.25 to 0.55) as well as a significant improvement in other secondary outcomes (quality of life, BMI, sweat chloride concentration) when compared to placebo.[3]

There are many limitations increasing the risk of bias in this study and decreasing the applicability. It is unknown how many subjects achieved a clinically significant change in quality of life, as measured by the CFQ-R domain, and there is insufficient information to assess the severity of the exacerbations detected. Pulmonary exacerbations were reported as an annualized estimated event rate based on 48 weeks even though only 24 weeks of data is available.

Additionally, the enrolled population only included 79 different MF mutations with the majority having a Class I mutation (78%). Therefore, clinical data is not available for all CFTR mutations in the FDA approved indication. There was a 28-day screening period prior to randomization and no information is available on

how many subjects failed to meet randomization criteria during this screening period. The FDA recommended including ELX/IVA as a treatment arm to evaluate the benefit of adding a second corrector.[12] However, this was not included and we cannot assess the contribution of ELX or TEZ to the combination. Lastly, there was a difference of 5% or greater between the treatment arms in concomitant medication use for 13 medications, including inhaled sodium chloride, tobramycin and other medications.

The second trial by Heijerman et al. included only those who are homozygous for the F508del mutation.[3] It compared ELX/TEZ/IVA to TEZ/IVA for 4 weeks of therapy. Treatment with ELX/TEZ/IVA resulted in statistically significant improvements in ppFEV1 at week 4 compared to TEZ/IVA. The LS mean treatment difference for the ELX/TEZ/IVA group versus TEZ/IVA group for the change from baseline in ppFEV1 at week 4 was 10.0% (95% CI 7.4% to 12.6%; p<0.0001).[4] There was an absolute increase in ppFEV1 of 0.4% in the TEZ/IVA and 10.4% in the ELX/TEZ/IVA arm. This trial was too short in duration to evaluate other clinically important outcomes, including pulmonary exacerbations.

The trial population had a mean baseline ppFEV1 of 60.9% and CFQ-R score of 71.5 (range 0 to 100 with higher scores indicating better health). The majority of enrolled patients were colonized by *Pseudomonas aeruginosa* (65%); however, numerically more ELX/TEZ/IVA subjects (71%) were colonized with *Pseudomonas aeruginosa* than TEZ/IVA subjects (60%). There were also small imbalances between the ELX/TEZ/IVA and TEZ/IVA arms with the use of hypertonic saline (69% vs. 79%), inhaled corticosteroids (65% vs. 54%) and azithromycin (60% vs. 48%) between the 2 trial arms, respectively, increasing the risk of selection bias. Previous studies evaluating TEZ/IVA in those homozygous for F508del mutation demonstrated a 3.4% increase in ppFEV1, which is larger than the minor change of 0.4% in this trial. This trial also included a 28-day screening period followed by a 28-day run in period with TEZ/IVA, further limiting the applicability of these results to the general population.

Clinical Safety:
The most common adverse drug reactions to ELX/TEZ/IVA (occurring in ≥5% of patients and at a frequency higher than placebo by ≥1%) are included in **Table 3.** Some type of skin related adverse event was experienced by 23% of subjects in the ELX/TEV/IVA arm, compared to 14% in the placebo arm. These reactions included rash, pruritis, and hypersensitivity reaction compared to 14% in the placebo arm.

Table 3: Common Adverse Drug Reactions[26]

Adverse Drug Reactions (Preferred Term)	TRIKAFTA N=202 n (%)	Placebo N=201 n (%)
Headache	35 (17)	30 (15)
Upper respiratory tract infection[a]	32 (16)	25 (12)
Abdominal pain[b]	29 (14)	18 (9)
Diarrhea	26 (13)	14 (7)
Rash[c]	21 (10)	10 (5)
Alanine aminotransferase increased	20 (10)	7 (3)
Nasal congestion	19 (9)	15 (7)
Blood creatine phosphokinase increased	19 (9)	9 (4)
Aspartate aminotransferase increased	19 (9)	4 (2)
Rhinorrhea	17 (8)	6 (3)
Rhinitis	15 (7)	11 (5)
Influenza	14 (7)	3 (1)
Sinusitis	11 (5)	8 (4)
Blood bilirubin increased	10 (5)	2 (1)

a Includes upper respiratory tract infection and viral upper respiratory tract infection
b Includes abdominal pain, abdominal pain upper, abdominal pain lower
c Includes: rash, rash generalized, rash erythematous, rash macular, rash pruritic

However, the short duration of these trials makes it difficult to evaluate adverse events. The severe adverse events that did occur suggest the potential for clinically significant elevations in liver transaminases and creatinine kinase abnormalities. The FDA reviewer noted that the data suggest an imbalance in elevations of liver enzymes and bilirubin in the ELX/TEZ/IVA arm compared to placebo and TEZ/IVA.[12] Additionally, ELX/TEZ/IVA has not been studied in patients with moderate or severe hepatic impairment and is not recommended in this population. All 3 drug components are extensively metabolized by CYP3A4 and should not be used with strong inhibitors or inducers of CYP3A4.

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 ppFEV1 from baseline at week 4

Table 4. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Elexacaftor and tezacaftor facilitate the cellular processing and trafficking of normal and select mutant forms of cystic fibrosis transmembrane conductance regulator (CFTR) (including F508del-CFTR) to increase the amount of mature CFTR protein delivered to the

	cell surface. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface.
Oral Bioavailability	Elexacaftor 80% Tezacaftor and Ivacaftor: Not determined
Distribution	Elexacaftor: 53.7 L, Tezacaftor: 82 L, Ivacaftor 293 L
Protein Binding	Elexacaftor > 99%, Tezacaftor and Ivacaftor: ~99%
Elimination	Elexacaftor: Urine 0.23%, feces ~87% as metabolites; Tezacaftor: urine 6.6%, feces: ~88%; Ivacaftor: urine 14%, feces 72%
Half-Life	Elexacaftor: 29.8 hours, Tezacaftor: 17.4 hours, Ivacaftor: 15 hours
Metabolism	CYP3A4/5 to active metabolites

Table 5. 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. Heijerman et al.[4] Phase 3, MC, DB, AC, RCT	1. ELX/TEZ/IVA (200 mg QDay/200 mg QDay/150 mg BID) 2. TEZ/IVA (100 mg QDay/150 mg BID) Following a 4-week screening period and a 4-week run in period with TEZ/IVA Duration: 4 weeks	Demographics: • 55% female • Mean 28 y/o • 72% ≥ 18 y/o • 65% *P. aeruginosa* • Baseline ppFEV1 61% Key Inclusion Criteria: •≥ 12 years •CF homozygous for F508del •FEV_1 40-90% •stable CF Key Exclusion Criteria: •Cirrhosis •solid organ transplant, alcohol or drug abuse in past year, cancer, hemolysis, G6PD deficiency •hemoglobin < 10 g/dl, total bilirubin ≥ 2 X ULN, AST/ALT ≥ 3 ULN, GFR < 50 ml/min •lung infection with organisms associated with rapid decline •moderate and strong CYP3A4 inducers and inhibitors	ITT: 1. 55 2. 52 PP: 1. 55 2. 52 Attrition: 1. 1 2. 0	Primary Endpoint: Absolute change in ppFEV1 at week 4 1. 10.4% 2. 0.4% Difference 10% (95%CI 7.4 to 12.6) P<0.0001 Secondary Endpoints: Absolute change in CFQ-R respiratory domain at week 4: 1. 16 2. -1.4 Difference 17.4 points; 95% CI 11.8 to 23) P<0.0001	N/A N/A	Discontinuations due to adverse effects: 1. 0 (0%) 2. 0 (0%) Pulmonary exacerbations: 1. 1 (2%) 2. 6 (12%) p-values not reported	NS NA	**Risk of Bias (low/high/unclear)**: Selection Bias: unclear: interactive web response system used for randomization. Difference in *P. aeruginosa* positive and baseline medications, including previous CFTR modulator therapy, at baseline. Performance Bias: low: double dummy design Detection Bias: unclear: unclear blinding for outcome assessors Attrition Bias: low: mIIT used for efficacy analysis. Very low attrition overall. Reporting Bias: High: Unclear how many subjects did not meet randomization criteria from screening period Other Bias: High: Designed by Vertex Pharmaceuticals. Vertex performed data gathering, analysis, and writing of the manuscript. **Applicability**: Patient: Extensive exclusion criteria limits generalizability including significant comorbidity left up to the discretion of the provider, limited subjects included with severe disease (FEV_1 < 40%) or with FEV_1 > 90%, screening and run in periods limits applicability Intervention: Not a clear dose response seen in phase 2 trials. However, the highest dose, 200 mg, was chosen for phase 3. Comparator: TEZ/IVA is approved for treatment of CF in the homozygous F508del population and is an appropriate active control for the study Outcomes: FEV_1 is a surrogate outcome. There is no agreed upon difference clinically meaningful difference and it has not been established that changes in FEV_1 translate to long term clinical benefits. Additionally 4 weeks is not long enough to evaluate clinically significant outcomes. Setting: 44 sites in four countries (Belgium, Netherlands, UK, U.S.); 63% in North America.

2.Middleton, et al.[3] Phase 3, MC, DB, AC, RCT	1. ELX/TEZ/IVA (200 mg QDay/200 mg QDay/150 mg BID) 2. placebo Following a 28-day screening period Duration: 24-weeks	Demographics: • 48% female • Mean 26 y/o • 70% ≥ 18 y/o • 71% *Pseudomonas* • Baseline ppFEV1 61.4% Key Inclusion Criteria: • ≥ 12 years • heterozygous for F508del and an MF mutation* • FEV1 40-90% • stable CF Key Exclusion Criteria: See Heijerman et al	ITT: 1. 200 2. 203 PP: 1. 197 2. 203 Attrition: 1. 4 2. 1	Primary Endpoint: Absolute change in ppFEV1 at week 4 1. 13.6% 2. -0.2% Difference 13.8% (95%CI 12.1 to 15.4) P<0.001 Secondary Endpoints: Total Number of Pulmonary exacerbations (estimated event rate/year) 1. 41 (0.37) 2. 113 (0.98) Rate Ratio 0.37 (95% CI 0.25 to 0.55) P<0.001 Number of subjects with pulmonary exacerbations: 1. 31 (15.5%) 2. 76 (37.4%)	NA NA ARR 21.9%/ NNT 5	Discontinuations due to adverse effects: 1. 3 (2%) 2. 0 (0%) Infective pulmonary exacerbation: 1. 44 (21.8%) 2. 95 (47.3%) Serious adverse event: 1. 28 (13.9%) 2. 42 (20.9%)		**Risk of Bias (low/high/unclear)**: Selection Bias: unclear: interactive web response system used for randomization. Some differences in baseline prior medications used and *P. aeruginosa* history Performance Bias: low: double-blinded to subjects and study team, double-dummy design Detection Bias: unclear: blinded to site monitor and study team. Unclear if centralized spirometry service used was blinded. Attrition Bias: low: mIIT used for efficacy analysis. Very low attrition overall. Reporting Bias: High: Unclear how many subjects did not meet randomization criteria from screening period Other Bias: High: Designed by Vertex Pharmaceuticals. Vertex performed data gathering, analysis, and writing of the manuscript. **Applicability**: Patient: See Heijerman et al. Intervention: See Heijerman et al. Comparator: Lack of approved CFTR modulator in this population so placebo used. However, FDA recommended an ELX/IVA treatment arm, which was not included. Outcomes: FEV_1 is a surrogate outcome. There is no agreed upon difference clinically meaningful difference and it has not been established that changes in FEV_1 translate to long term clinical benefits. Setting: Multicenter (59% in North America and 41% Europe)

Abbreviations [alphabetical order]: AC = active comparator; AE = adverse events; ALT = alanine aminotransferase; ARR = absolute risk reduction; AST = aspartate aminotransferase; BID = twice daily; CI = confidence interval; CF = cystic fibrosis; CFQ-R = cystic fibrosis questionnaire – revised; CFTR = cystic fibrosis transmembrane conductance regulator; CV = cardiovascular; DB = double blind; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; G6PD = glucose-6-phosphate dehydrogenase; GFR = glomerular filtration rate; ITT = intention to treat; HTN = hypertension; IVA = IVA; LSM = least squares mean difference; MC = multicenter; MF = minimal function; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = non-significant; PC = placebo controlled; PG = parallel group; PP = per protocol; $ppFEV_1$ = percent predicted forced expiratory volume in one second; QDay = daily; RCT = randomized controlled trial; ULN = upper limit of normal; yr = year

*Minimal Function mutations included in **Appendix 4**

References:

1. 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).* 2014;18(18):1-106.
2. 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.* 2013;187(7):680-689.
3. Kumar S, Tana A, Shankar A. Cystic fibrosis--what are the prospects for a cure? *European journal of internal medicine.* 2014;25(9):803-807.
4. O'Reilly R, Elphick HE. Development, clinical utility, and place of ivacaftor in the treatment of cystic fibrosis. *Drug design, development and therapy.* 2013;7:929-937.
5. 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.* 2015;3(7):524-533.
6. Flume PA, Liou TG, Borowitz DS, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest.* 2012;142(3):718-724.
7. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. *The New England journal of medicine.* 2017;377(21):2024-2035.
8. 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.
9. 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.
10. 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.* 2010;9(4):250-256.
11. 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.* 2013;143(1):14-18.
12. 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.* 2009;135(6):1610-1618.
13. Mayer-Hamblett N, Boyle M, VanDevanter D. Advancing clinical development pathways for new CFTR modulators in cystic fibrosis. *Thorax.* 2016;71(5):454-461.
14. Vertex Pharmaceuticals. Kalydeco (ivacaftor) Prescribing Information. May 2017. http://pi.vrtx.com/files/uspi_ivacaftor.pdf. Accessed November 5, 2017.
15. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *The New England journal of medicine.* 2011;365(18):1663-1672.
16. Patel S, Sinha IP, Dwan K, Echevarria C, Schechter M, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *The Cochrane database of systematic reviews.* 2015(3):Cd009841.

17. Pettit RS. Cystic fibrosis transmembrane conductance regulator-modifying medications: the future of cystic fibrosis treatment. *The Annals of pharmacotherapy.* 2012;46(7-8):1065-1075.
18. Wainwright CE, Elborn JS, Ramsey BW. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. *The New England journal of medicine.* 2015;373(18):1783-1784.
19. Boyle MP, Bell SC, Konstan MW, et al. A CFTR corrector (lumacaftor) and a CFTR potentiator (ivacaftor) for treatment of patients with cystic fibrosis who have a phe508del CFTR mutation: a phase 2 randomised controlled trial. *The Lancet Respiratory medicine.* 2014;2(7):527-538.
20. Orkambi Prescribing Information. Prescribing Information. Vertex Pharmaceuticals. Boston, MA 02210. September 2016. http://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf.
21. 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.* 2017;377(21):2013-2023.
22. Trikafta Prescribing Information. Vertex Pharmaceuticals. Boston, MA. January 2020. Available at: https://pi.vrtx.com/files/uspi_elexacaftor_tezacaftor_ivacaftor.pdf.
23. Skilton M, Krishan A, Patel S, Sinha IP, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *The Cochrane database of systematic reviews.* 2019;1:Cd009841.
24. Southern KW, Patel S, Sinha IP, Nevitt SJ. Correctors (specific therapies for class II CFTR mutations) for cystic fibrosis. *The Cochrane database of systematic reviews.* 2018;8:Cd010966.
25. 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).* 2019;394(10212):1940-1948.
26. 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.* 2019;381(19):1809-1819.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
dornase alfa	PULMOZYME	SOLUTION	IH	Y
sodium chloride for inhalation	SODIUM CHLORIDE	VIAL-NEB	IH	Y
tobramycin/nebulizer	KITABIS PAK	AMPUL-NEB	IH	Y
tobramycin/nebulizer	TOBRAMYCIN	AMPUL-NEB	IH	Y
aztreonam lysine	CAYSTON	VIAL-NEB	IH	N
ivacaftor	KALYDECO	GRAN PACK	PO	N
ivacaftor	KALYDECO	TABLET	PO	N
lumacaftor/ivacaftor	ORKAMBI	GRAN PACK	PO	N
lumacaftor/ivacaftor	ORKAMBI	TABLET	PO	N
tezacaftor/ivacaftor	SYMDEKO	TABLET SEQ	PO	N
tobramycin	BETHKIS	AMPUL-NEB	IH	N
tobramycin	TOBI PODHALER	CAP W/DEV	IH	N
tobramycin	TOBI PODHALER	CAPSULE	IH	N
tobramycin in 0.225% sod chlor	TOBI	AMPUL-NEB	IH	N
tobramycin in 0.225% sod chlor	TOBRAMYCIN	AMPUL-NEB	IH	N
amikacin liposomal/neb.accessr	ARIKAYCE	VIAL-NEB	IH	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 3 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 10, 2014

1 Cystic Fibrosis Transmembrane Conductance Regulator 8908
2 elexacaftor.mp. 6
3 ivacaftor.mp. 640
4 lumacaftor.mp 321
5 tezacaftor.mp. 61
6 CFTR potentiators.mp. 70
7 CFTR correctors.mp. 73
8 cystic fibrosis.mp. or Cystic Fibrosis/ 5—18
9 1 or 2 or 3 or 4 or 5 or 6 or 7 9208
10 8 and 9 9171
11 limit 10 to (English language and full text and humans and yr="2018-Current" and (clinical trial, phase III or clinical trial, phase iv or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or "systematic review")) 4

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRIKAFTA safely and effectively. See full prescribing information for TRIKAFTA.

TRIKAFTA™ (elexacaftor, tezacaftor and ivacaftor tablets; ivacaftor tablets), co-packaged for oral use
Initial U.S. Approval: 2019

----------INDICATIONS AND USAGE----------
TRIKAFTA is a combination of ivacaftor, a CFTR potentiator, tezacaftor, and elexacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the *CFTR* gene.
If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one *F508del* mutation. (1)

----------DOSAGE AND ADMINISTRATION----------
- Adults and pediatric patients aged 12 years and older:
  - Morning dose: two elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg tablets
  - Evening dose: one ivacaftor 150 mg tablet
  - Morning and evening dose should be taken approximately 12 hours apart with fat-containing food. (2.1, 12.3)
- Should not be used in patients with severe hepatic impairment. Use not recommended in patients with moderate hepatic impairment unless the benefit exceeds the risk. Reduce dose if used in patients with moderate hepatic impairment. Liver function tests should be closely monitored. (2.2, 5.1, 8.7, 12.3)
- Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors. (2.3, 5.3, 7.2, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: fixed dose combination containing elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg.

Co-packaged with:
- Tablets: ivacaftor 150 mg. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Elevated liver function tests (ALT, AST or bilirubin): Liver function tests (ALT, AST, and bilirubin) should be assessed prior to initiating TRIKAFTA, every 3 months during the first year of treatment, and annually thereafter. In patients with a history of hepatobiliary disease or liver function test elevations, more frequent monitoring should be considered. Dosing should be interrupted in patients with ALT or AST >5 x upper limit of normal (ULN) or ALT or AST >3 x ULN with bilirubin >2 x ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming treatment. (5.1, 6)
- Use with CYP3A inducers: Concomitant use with strong CYP3A inducers (e.g., rifampin, St. John's wort) significantly decrease ivacaftor exposure and are expected to decrease elexacaftor and tezacaftor exposure, which may reduce TRIKAFTA efficacy. Therefore, co-administration is not recommended. (5.2, 7.1, 12.3)
- Cataracts: Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor-containing regimens. Baseline and follow-up examinations are recommended in pediatric patients initiating TRIKAFTA treatment. (5.4, 8.4)

----------ADVERSE REACTIONS----------
The most common adverse drug reactions to TRIKAFTA (occurring in ≥5% of patients and at a frequency higher than placebo by ≥1%) were headache, upper respiratory tract infection, abdominal pain, diarrhea, rash, alanine aminotransferase increased, nasal congestion, blood creatine phosphokinase increased, aspartate aminotransferase increased, rhinorrhea, rhinitis, influenza, sinusitis and blood bilirubin increased. (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 CYP3A inducers: Avoid co-administration. (5.2, 7.1, 12.3)
- Strong or moderate CYP3A inhibitors: Reduce TRIKAFTA dosage when co-administered. Avoid food or drink containing grapefruit. (2.3, 5.3, 7.2, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2019

Appendix 4: Minimal Function Mutations

Minimal Function Mutation Category		Mutation				
Class I mutations (absence of CFTR protein production)	Nonsense mutations	Q2X	L218X	Q525X	R792X	E1104X
		S4X	Q220X	G542X	E822X	W1145X
		W19X	Y275X	G550X	W882X	R1158X
		G27X	C276X	Q552X	W846X	R1162X
		Q39X	Q290X	R553X	Y849X	S1196X
		W57X	G330X	E585X	R851X	W1204X
		E60X	W401X	G673X	Q890X	L1254X
		R75X	Q414X	Q685X	S912X	S1255X
		L88X	S434X	R709X	Y913X	W1282X
		E92X	S466X	K710X	Q1042X	Q1313X
		Q98X	S489X	Q715X	W1089X	Q1330X
		Y122X	Q493X	L732X	Y1092X	E1371X
		E193X	W496X	R764X	W1098X	Q1382X
		W216X	C524X	R785X	R1102X	Q1411X
	Canonical splice mutations	185+1G→T	711+5G→A	1717-8G→A	2622+1G→A	3121-1G→A
		296+1G→A	712-1G→T	1717-1G→A	2790-1G→C	3500-2A→G
		296+1G→T	1248+1G→A	1811+1G→C	3040G→C (G970R)	3600+2insT
		405+1G→A	1249-1G→A	1811+1.6kbA→G	3850-1G→A	
		405+3A→C	1341+1G→A	1811+1643G→T	3120G→A	4005+1G→A
		406-1G→A	1525-2A→G	1812-1G→A	3120+1G→A	4374+1G→T
		621+1G→T	1525-1G→A	1898+1G→A	3121-2A→G	
		711+1G→T	1898+1G→C			

	Small (≤3 nucleotide) insertion/deletion (ins/del) frameshift mutations	182delT	1078delT	1677delTA	2711delT	3737delA
		306insA	1119delA	1782delA	2732insA	3791delC
		306delTAGA	1138insG	1824delA	2869insG	3821delT
		365-366insT	1154insTC	1833delT	2896insAG	3876delA
		394delTT	1161delC	2043delG	2942insT	3878delG
		442delA	1213delT	2143delT	2957delT	3905insT
		444delA	1259insA	2183AA→G*	3007delG	4016insT
		457TAT→G	1288insTA	2184delA	3028delA	4021dupT
		541delC	1343delG	2184insA	3171delC	4022insT
		574delA	1471delA	2307insA	3171insC	4040delA
		663delT	1497delGG	2347delG	3271delGG	4279insA
		849delG	1548delG	2585delT	3349insT	4326delTC
		935delA	1609del CA	2594delGT	3659delC	
	Non-small (>3 nucleotide) insertion/deletion (ins/del) frameshift mutations	CFTRdele1	CFTRdele16-17b	1461ins4		
		CFTRdele2	CFTRdele17a,17b	1924del7		
		CFTRdele2,3	CFTRdele17a-18	2055del9→A		
		CFTRdele2-4	CFTRdele19	2105-2117del13insAGAAA		
		CFTRdele3-10,14b-16	CFTRdele19-21	2372del8		
		CFTRdele4-7	CFTRdele21	2721del11		
		CFTRdele4-11	CFTRdele22-24	2991del32		
		CFTR50kbdel	CFTRdele22,23	3121-977_3499+248del2515		
		CFTRdup6b-10	124del23bp	3667ins4		
		CFTRdele11	602del14	4010del4		
		CFTRdele13,14a	852del22	4209TGTT→AA		
		CFTRdele14b-17b	991del5			
Missense and in-frame deletion mutations	Missense mutations that are not responsive in vitro to tezacaftor, ivacaftor, or tezacaftor/ivacaftor	A46D†	V520F	Y569D†	N1303K	
		G85E	A559T†	L1065P		
		R347P	R560T	R1066C		
		L467P†	R560S	L1077P†		
		I507del	A561E	M1101K		

Appendix 5: Prior Authorization Criteria

Oral Cystic Fibrosis Modulators

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:

- 90 days to 6 months

Requires PA:

- Ivacaftor (Kalydeco®)
- Lumacaftor/Ivacaftor (Orkambi®)
- Tezacaftor/Ivacaftor (Symdeko®)
- Elxacaftor/Tezacaftor/Ivacaftor (Trikafta™)

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	≥ 6 months
Lumacaftor/ivacaftor (Orkambi)	Homozygous Phe508del	≥ 2 years
Tezacaftor/Ivacaftor (Symdeko)	Homozygous Phe508del, A455E, A1067T, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K,	≥ 6 years

	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	
Elexacaftor/tezacaftor/ivacaftor (Trikafta)	At least Phe508del mutation (homozygous or heterozygous)	≥ 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, or 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
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 #9

Approval Criteria		
7. What is the patient's baseline sweat chloride level?	Prescriber must provide documentation before approval. Document baseline value. Go to #8	
8. 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 #12 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).
9. Is the request for lumacaftor/ivacaftor?	**Yes:** Go to #10	**No:** Go to #11
10. Is the patient younger than 12 years of age?	**Yes:** Refer case to OHP Medical Director;	**No:** Go to #12
11. Is the request for tezacaftor/ivacaftor or elexacaftor/tezacaftor/ivacaftor?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Is the patient on ALL the following drugs, or has had an adequate trial of each drug, unless contraindicated or not appropriate based on age <6 years and normal lung function: • Dornase alfa; AND • Hypertonic saline; AND • Inhaled or oral antibiotics (if appropriate)?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. Is the patient on concomitant therapy with a strong CYP3A4 inducer (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14

Approval Criteria		
14. What are the baseline liver function (AST/ALT) and bilirubin levels (within previous 3 months)?	Document labs. Go to #15 If unknown, these labs need to be collected prior to approval.	
15. Is medication dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for 90 days. Note: Approve for 90 days to allow time for patient to have a sweat chloride test done after 30 days of treatment if on IVA (see **Renewal Criteria**). 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 this the first time the patient is requesting a renewal (after 90 days of initial approval)?	**Yes:** Go to #2	**No:** Go to #4
2. If prescription is for ivacaftor: Does the patient have a documented physiological response to therapy and evidence of adherence after 30 days of treatment, as defined by a sweat chloride test that has decreased by at least 20 mmol/L from baseline?	**Yes:** Go to #7	**No:** Go to #3 Consider patient's adherence to therapy and repeat test in 2 weeks to 45 days to allow for variability in test. If sodium chloride has still not decreased by 20 mmol/L, deny therapy for medical appropriateness

Renewal Criteria		
3. If the prescription is for lumacaftor/ivacaftor, tezacaftor/ivacaftor or elexacaftor/tezacaftor/ivacaftor: Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?	**Yes:** Go to #7	**No:** Pass to RPh; Deny (medical appropriateness)
4. Does the patient have documented response to therapy as defined as below : For patients age ≥6 years: • 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? For patients age 2-5 years (cannot complete lung function tests) • Significant improvement in BMI by 10% from baseline; OR • Improvement in exacerbation frequency or severity; OR • Sweat chloride test has decreased from baseline by 20 mmol/L from baseline?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient been compliant with therapy, as determined by refill claims history?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Have liver function tests been appropriately monitored? What are the most recent liver function tests (AST, ALT, and bilirubin)? Note: Monitoring LFTs is recommended every 3 months for the first year, followed by once a year.	Document. Go to #7 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.	

Renewal Criteria		
7. Is the CFTR modulator dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for additional 3 months (total of 6 months since start of therapy)	**No:** Pass to RPh. Deny; medical appropriateness

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 1 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.
- 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	

<u>Lumacaftor/ivacaftor</u>

- 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.

<u>Tezacaftor/ivacaftor:</u>

- 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.

P&T Review: *9/19 (MH); 9/18; 7/18; 11/16; 11/15; 7/15; 5/15; 5/14; 6/12*
Implementation: *11/1/19; 11/1/2018; 1/1/16; 8/25/15; 8/12*