Drugs of Cystic Fibrosis Modulators

Date of Review: April 2020

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

Author: Megan Herink, PharmD
• 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).
• Update prior authorization criteria for initial approval of 6 months and 12 months for subsequent approval (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.
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. 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. 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. 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. 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. There are three common alleles at the poly-T locus of the R117H gene (ST, 7T, 9T), with the 5T variant associated with greater severity of CF. 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. 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.

Table 1: CFTR mutation categories

<table>
<thead>
<tr>
<th>Class I: protein production mutations</th>
<th>Description</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class II: protein processing mutations</td>
<td>CFTR protein created, but misfolded, keeping it from reaching the cell surface</td>
<td>88%</td>
</tr>
<tr>
<td>Class III: gating mutations</td>
<td>CFTR protein created and reaches cell surface, but does not function properly</td>
<td>6%</td>
</tr>
<tr>
<td>Class IV: conduction mutations</td>
<td>Opening in CFTR protein ion channel is faulty</td>
<td>6%</td>
</tr>
<tr>
<td>Class V: insufficient protein mutations</td>
<td>CFTR created in insufficient quantities</td>
<td>5%</td>
</tr>
</tbody>
</table>

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. According to National Institute of Clinical Excellence (NICE), an absolute change in ppFEV₁ of 5% or more would be considered clinically important. 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. 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. 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%. 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. 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. 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. 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. Sweat chloride has been used as a biomarker for evaluation of change in CFTR activity in clinical trials of IVA. 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. 

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). 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). The most common gating mutations, G551D and R117H, represent approximately 7% of the U.S. CF population. In trials of patients with the G115D mutation, IVA increased FEV1 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. 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.

IVA is designed to increase the time that activated CFTR channels at the cell surface remain open.

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. 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. Phase 2 trials demonstrated lack of improvement in patients heterozygous for the F508del CFTR mutation. It is currently FDA-approved for those age 12 years and older who are homozygous for the F508del mutation in the CFTR gene. This patient group includes approximately 34% of the U.S. CF population. Studies of LUM/IVA did not demonstrate clinically significant results on meaningful outcomes. 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 (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. 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 ppFEV1 (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

<table>
<thead>
<tr>
<th>Generic Name (Brand)</th>
<th>FDA Approved Indication (in cystic fibrosis)</th>
<th>Specific Mutations Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elexacaftor/tezacaftor/ivacaftor26 (Trikafta®)</td>
<td>≥ 12 years who have at least one F508del mutation</td>
<td>See Appendix 4</td>
</tr>
</tbody>
</table>

### 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.2 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.

---

*Author: Megan Herink, Pharm.D.*

*April 2020*
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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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).\textsuperscript{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.\textsuperscript{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).
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.\textsuperscript{3,4} The primary outcome in both trials was the absolute change from baseline in ppFEV\textsubscript{1} 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.\textsuperscript{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.\textsuperscript{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 ppFEV\textsubscript{1} at week 4 compared to placebo with a LS mean treatment difference of 13.8\% (95\% CI 12.1 to 15.4; \textit{p}<0.0001).\textsuperscript{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.\textsuperscript{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. 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. 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). 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

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

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. 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               | 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.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Bioavailability</td>
<td>Elexacaftor 80% Tezacaftor and Ivacaftor: Not determined</td>
</tr>
<tr>
<td>Distribution</td>
<td>Elexacaftor: 53.7 L, Tezacaftor: 82 L, Ivacaftor 293 L</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>Elexacaftor &gt; 99%, Tezacaftor and Ivacaftor: ~99%</td>
</tr>
<tr>
<td>Elimination</td>
<td>Elexacaftor: Urine 0.23%, feces ~87% as metabolites; Tezacaftor: urine 6.6%, feces: ~88%; Ivacaftor: urine 14%, feces 72%</td>
</tr>
<tr>
<td>Half-Life</td>
<td>Elexacaftor: 29.8 hours, Tezacaftor: 17.4 hours, Ivacaftor: 15 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP3A4/5 to active metabolites</td>
</tr>
<tr>
<td>Ref./Study Design</td>
<td>Drug Regimens/Duration</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------</td>
</tr>
</tbody>
</table>
| 1. Heijerman et al.⁴ | 1. ELX/TEZ/IVA (200 mg QDay/200 mg QD/150 mg BID) | Demographics:  
- 55% female  
- Mean 28 y/o  
- 72% ≥ 18 y/o  
- 65% *P. aeruginosa*  
- Baseline ppFEV1 61%  
  | 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  
  | Discontinuations due to adverse effects:  
1. 0 (0%)  
2. 0 (0%)  
  Pulmonary exacerbations:  
1. 1 (2%)  
2. 6 (12%)  
  | N/A  
N/A  
  | N/A  
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: mITT 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.  
  | 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  
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: 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. 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.  
<p>| Author: Megan Herink, Pharm.D. | April 2020 |</p>
<table>
<thead>
<tr>
<th>Author: Megan Herink, Pharm.D.</th>
<th>April 2020</th>
</tr>
</thead>
</table>

2. Middleton, et al.³

Phase 3, MC, DB, AC, RCT

### Key Inclusion Criteria:
- ≥ 12 years
- heterozygous for F508del and an MF mutation*
- FEV1 40-90%
- stable CF

### Key Exclusion Criteria:
See Heijerman et al

### Demographics:
- 48% female
- Mean 26 y/o
- 70% ≥ 18 y/o
- 71% Pseudomonas
- Baseline ppFEV1 61.4%

### Duration:
24-weeks

### Placebo:
Following a 28-day screening period

### 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%)

### Attrition:
1. 4

2. 1

### 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: mITT 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: 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.
- 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
- FEV1 = 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
- ppFEV1 = 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:

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](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212273Orig1s000TOC.cfm).


**Appendix 1: Current Preferred Drug List**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Form</th>
<th>Route</th>
<th>PDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>dornase alfa</td>
<td>PULMOZYME</td>
<td>SOLUTION</td>
<td>IH</td>
<td>Y</td>
</tr>
<tr>
<td>sodium chloride for inhalation</td>
<td>SODIUM CHLORIDE</td>
<td>VIAL-NEB</td>
<td>IH</td>
<td>Y</td>
</tr>
<tr>
<td>tobramycin/nebulizer</td>
<td>KITABIS PAK</td>
<td>AMPUL-NEB</td>
<td>IH</td>
<td>Y</td>
</tr>
<tr>
<td>tobramycin/nebulizer</td>
<td>TOBRAMYCIN</td>
<td>AMPUL-NEB</td>
<td>IH</td>
<td>Y</td>
</tr>
<tr>
<td>aztreonam lysine</td>
<td>CAYSTON</td>
<td>VIAL-NEB</td>
<td>IH</td>
<td>N</td>
</tr>
<tr>
<td>ivacaftor</td>
<td>KALYDECO</td>
<td>GRAN PACK</td>
<td>PO</td>
<td>N</td>
</tr>
<tr>
<td>ivacaftor</td>
<td>KALYDECO</td>
<td>TABLET</td>
<td>PO</td>
<td>N</td>
</tr>
<tr>
<td>lumacaftor/ivacaftor</td>
<td>ORKAMBI</td>
<td>GRAN PACK</td>
<td>PO</td>
<td>N</td>
</tr>
<tr>
<td>lumacaftor/ivacaftor</td>
<td>ORKAMBI</td>
<td>TABLET</td>
<td>PO</td>
<td>N</td>
</tr>
<tr>
<td>tezacaftor/ivacaftor</td>
<td>SYMDEKO</td>
<td>TABLET SEQ</td>
<td>PO</td>
<td>N</td>
</tr>
<tr>
<td>tobramycin</td>
<td>BETHKIS</td>
<td>AMPUL-NEB</td>
<td>IH</td>
<td>N</td>
</tr>
<tr>
<td>tobramycin</td>
<td>TOBI PODHALER</td>
<td>CAP W/DEV</td>
<td>IH</td>
<td>N</td>
</tr>
<tr>
<td>tobramycin</td>
<td>TOBI PODHALER</td>
<td>CAPSULE</td>
<td>IH</td>
<td>N</td>
</tr>
<tr>
<td>tobramycin in 0.225% sod chlor</td>
<td>TOBI</td>
<td>AMPUL-NEB</td>
<td>IH</td>
<td>N</td>
</tr>
<tr>
<td>tobramycin in 0.225% sod chlor</td>
<td>TOBRAMYCIN</td>
<td>AMPUL-NEB</td>
<td>IH</td>
<td>N</td>
</tr>
<tr>
<td>amikacin liposomal/neb.accessr</td>
<td>ARIKAYCE</td>
<td>VIAL-NEB</td>
<td>IH</td>
<td></td>
</tr>
</tbody>
</table>
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™ (elixacaftor, 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 elixacaftor 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:
  o Morning dose: two elixacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg tablets
  o Evening dose: one ivacaftor 150 mg tablet
  o 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)

DOSE FORMS AND STRENGTHS
• Tablets: fixed dose combination containing elixacaftor 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 elixacaftor 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

<table>
<thead>
<tr>
<th>Minimal Function Mutation Category</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I mutations</td>
<td></td>
</tr>
<tr>
<td>(absence of CFTR protein production)</td>
<td></td>
</tr>
<tr>
<td>Nonsense mutations</td>
<td>Q2X L218X Q525X R792X E1104X</td>
</tr>
<tr>
<td>S4X Q220X G542X E822X W1145X</td>
<td></td>
</tr>
<tr>
<td>W19X Y275X G550X W882X R1158X</td>
<td></td>
</tr>
<tr>
<td>G27X C276X Q552X W846X R1162X</td>
<td></td>
</tr>
<tr>
<td>Q39X Q290X R553X Y849X S1196X</td>
<td></td>
</tr>
<tr>
<td>W57X G330X E555X R851X W1204X</td>
<td></td>
</tr>
<tr>
<td>E60X W401X G673X Q890X L1254X</td>
<td></td>
</tr>
<tr>
<td>R75X Q414X Q685X S912X S1255X</td>
<td></td>
</tr>
<tr>
<td>L88X S434X R709X Y913X W1282X</td>
<td></td>
</tr>
<tr>
<td>E92X S466X K710X Q1042X Q1313X</td>
<td></td>
</tr>
<tr>
<td>Q98X S489X Q715X W1089X Q1330X</td>
<td></td>
</tr>
<tr>
<td>Y122X Q493X L732X Y1092X E1371X</td>
<td></td>
</tr>
<tr>
<td>E193X W496X R764X W1098X Q1382X</td>
<td></td>
</tr>
<tr>
<td>W216X C524X R785X R102X Q1411X</td>
<td></td>
</tr>
<tr>
<td>Canonical splice mutations</td>
<td>185+1G→T 711+5G→A 1717-8G→A 2622+1G→A 3121-1G→A</td>
</tr>
<tr>
<td>296+1G→A 712+1G→T 1717-1G→A 2790-1G→C 3500-2A→G</td>
<td></td>
</tr>
<tr>
<td>296+1G→T 1248+1G→A 1811+1G→C 3040G→C 3600+2insT</td>
<td></td>
</tr>
<tr>
<td>(G970R) 405+1G→A 1249-1G→A 1811+1.6kbA→G 3850-1G→A</td>
<td></td>
</tr>
<tr>
<td>405+3A→C 1341+1G→A 1811+1643G→T 3120G→A 4005+1G→A</td>
<td></td>
</tr>
<tr>
<td>406-1G→A 1525-2A→G 1812-1G→A 3120+1G→A 4374+1G→T</td>
<td></td>
</tr>
<tr>
<td>621+1G→T 1525-1G→A 1898+1G→A 3121-2A→G</td>
<td></td>
</tr>
<tr>
<td>711+1G→T 1898+1G→C</td>
<td></td>
</tr>
</tbody>
</table>

Author: Megan Herink, Pharm.D.  April 2020
<table>
<thead>
<tr>
<th>Small (≤3 nucleotide) insertion/deletion (ns/del) frameshift mutations</th>
<th>18delI</th>
<th>10/8delI</th>
<th>15/6delI A</th>
<th>2/11delI</th>
<th>3/3delA</th>
</tr>
</thead>
<tbody>
<tr>
<td>306insA</td>
<td>1119delA</td>
<td>1782delA</td>
<td>2732insA</td>
<td>3791delC</td>
<td></td>
</tr>
<tr>
<td>306delTAGA</td>
<td>1138insG</td>
<td>1824delA</td>
<td>2869insG</td>
<td>3821delT</td>
<td></td>
</tr>
<tr>
<td>365-368insT</td>
<td>1154insTC</td>
<td>1833delT</td>
<td>2896insAG</td>
<td>3876delA</td>
<td></td>
</tr>
<tr>
<td>394delTT</td>
<td>1161delC</td>
<td>2043delG</td>
<td>2942insT</td>
<td>3878delG</td>
<td></td>
</tr>
<tr>
<td>442delA</td>
<td>1213delT</td>
<td>2143delT</td>
<td>2957delT</td>
<td>3905insT</td>
<td></td>
</tr>
<tr>
<td>444delA</td>
<td>1259insA</td>
<td>2183AA→G*</td>
<td>3007delG</td>
<td>4016insT</td>
<td></td>
</tr>
<tr>
<td>457TAT→G</td>
<td>1288insTA</td>
<td>2184delA</td>
<td>3028delIA</td>
<td>4021dupT</td>
<td></td>
</tr>
<tr>
<td>541delC</td>
<td>1343delG</td>
<td>2184insA</td>
<td>3171delC</td>
<td>4022insT</td>
<td></td>
</tr>
<tr>
<td>574delA</td>
<td>1471delA</td>
<td>2307insA</td>
<td>3171insC</td>
<td>4040delA</td>
<td></td>
</tr>
<tr>
<td>663delT</td>
<td>1497delGG</td>
<td>2347delG</td>
<td>3271delGG</td>
<td>4279insA</td>
<td></td>
</tr>
<tr>
<td>849delG</td>
<td>1548delG</td>
<td>2585delT</td>
<td>3349insT</td>
<td>4326delTC</td>
<td></td>
</tr>
<tr>
<td>935delA</td>
<td>1609del CA</td>
<td>2594delGT</td>
<td>3659delC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-small (&gt;3 nucleotide) insertion/deletion (ns/del) frameshift mutations</th>
<th>CFTRdele1</th>
<th>CFTRdele16-17b</th>
<th>1461ins4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFTRdele2</td>
<td>CFTRdele17a,17b</td>
<td>1924del7</td>
<td></td>
</tr>
<tr>
<td>CFTRdele2,3</td>
<td>CFTRdele17a-18</td>
<td>2055del9→A</td>
<td></td>
</tr>
<tr>
<td>CFTRdele2-4</td>
<td>CFTRdele19</td>
<td>2105-2117del13insAGAAA</td>
<td></td>
</tr>
<tr>
<td>CFTRdele3-10,14b-16</td>
<td>CFTRdele19-21</td>
<td>2372del8</td>
<td></td>
</tr>
<tr>
<td>CFTRdele4-7</td>
<td>CFTRdele21</td>
<td>2721del11</td>
<td></td>
</tr>
<tr>
<td>CFTRdele4-11</td>
<td>CFTRdele22-24</td>
<td>2991del32</td>
<td></td>
</tr>
<tr>
<td>CFTR50kdel</td>
<td>CFTRdele22,23</td>
<td>3121-977_3499+248del2515</td>
<td></td>
</tr>
<tr>
<td>CFTRdup6b-10</td>
<td>124del23bp</td>
<td>3667ins4</td>
<td></td>
</tr>
<tr>
<td>CFTRdele11</td>
<td>602del14</td>
<td>4010del4</td>
<td></td>
</tr>
<tr>
<td>CFTRdele13,14a</td>
<td>852del22</td>
<td>4200TGGTT→AA</td>
<td></td>
</tr>
<tr>
<td>CFTRdele14b-17b</td>
<td>991delE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Missense and in-frame deletion mutations</th>
<th>Missense mutations that are not responsive in vitro to tezacaftor, ivacaftor, or tezacaftor/ivacaftor</th>
</tr>
</thead>
<tbody>
<tr>
<td>A46D†</td>
<td>V520F</td>
</tr>
<tr>
<td>G85E</td>
<td>A559T†</td>
</tr>
<tr>
<td>R347P</td>
<td>R560T</td>
</tr>
<tr>
<td>L467P†</td>
<td>R660S</td>
</tr>
<tr>
<td>I507del</td>
<td>A561E</td>
</tr>
</tbody>
</table>
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®)
- Elexacaftor/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

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>FDA approved CFTR mutation</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumacaftor/Ivacaftor (Orkambi)</td>
<td>Homozygous Phe508del</td>
<td>≥ 2 years</td>
</tr>
<tr>
<td>Tezacaftor/Ivacaftor (Symdeko)</td>
<td>Homozygous Phe508del, A455E, A1067T, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K,</td>
<td>≥ 6 years</td>
</tr>
<tr>
<td>Elexacaftor/tezacaftor/ivacaftor (Trikafta)</td>
<td>At least Phe508del mutation (homozygous or heterozygous)</td>
<td>≥ 12 years</td>
</tr>
</tbody>
</table>

<p>| 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)? | <strong>Yes</strong>: Go to Renewal Criteria | <strong>No</strong>: Go to #2 |
| 2. Does the patient have a diagnosis of Cystic Fibrosis? | Yes: Record ICD10 code. Go to #3 | <strong>No</strong>: Pass to RPh. Deny; medical appropriateness |
| 3. Is the request from a practitioner at an accredited Cystic Fibrosis Center or a pulmonologist? | <strong>Yes</strong>: Go to #4 | <strong>No</strong>: Pass to RPh. Deny; medical appropriateness |
| 4. Is the request for an FDA approved age and CFTR gene mutation as defined in Table 1? | <strong>Yes</strong>: Go to #5 | <strong>No</strong>: 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? | <strong>Yes</strong>: Go to #7 | <strong>No</strong>: Go to #9 |</p>
<table>
<thead>
<tr>
<th>Approval Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. What is the patient's baseline sweat chloride level?</td>
</tr>
</tbody>
</table>
| 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 6 months.**  
Note: Approve for 6 months 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

<table>
<thead>
<tr>
<th>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?</th>
<th><strong>Yes:</strong> Go to #7</th>
<th><strong>No:</strong> Pass to RPh; Deny (medical appropriateness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Does the patient have documented response to therapy as defined as below:</td>
<td><strong>Yes:</strong> Go to #5</td>
<td><strong>No:</strong> Pass to RPh. Deny; medical appropriateness</td>
</tr>
<tr>
<td>For patients age ≥6 years:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• An improvement or lack of decline in lung function as measured by the FEV1 when the patient is clinically stable; OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• A reduction in the incidence of pulmonary exacerbations; OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• A significant improvement in BMI by 10% from baseline?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For patients age 2-5 years (cannot complete lung function tests)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Significant improvement in BMI by 10% from baseline; OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Improvement in exacerbation frequency or severity; OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sweat chloride test has decreased from baseline by 20 mmol/L from baseline?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Has the patient been compliant with therapy, as determined by refill claims history?</td>
<td><strong>Yes:</strong> Go to #6</td>
<td><strong>No:</strong> Pass to RPh. Deny; medical appropriateness</td>
</tr>
<tr>
<td>6. Have liver function tests been appropriately monitored? What are the most recent liver function tests (AST, ALT, and bilirubin)?</td>
<td>Document. Go to #7</td>
<td></td>
</tr>
<tr>
<td>Note: Monitoring LFTs is recommended every 3 months for the first year, followed by once a year.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Note: Therapy should be interrupted in patients with AST or ALT &gt;5x the upper limit of normal (ULN), or ALT or AST &gt;3x ULN with bilirubin &gt;2x ULN.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 12 months | 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 6 months to < 6 years
      - with body weight < 14 kg: 50 mg packet once daily
      - with body weight ≥ 14 kg: 75 mg packet of oral 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>
<thead>
<tr>
<th>Drug co-administered with IVA</th>
<th>Co-administered drug category</th>
<th>Recommended dosage adjustment for IVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>CYP3A4 strong inhibitors</td>
<td>Reduce IVA dose to 1 tablet or 1 packet of oral granules <strong>twice weekly</strong> (one-seventh of normal initial dose)</td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telithromycin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Examples of CYP3A4 inhibitors and inducers.
<table>
<thead>
<tr>
<th>Fluconazole</th>
<th>Erythromycin</th>
<th>Clofazimine</th>
<th>CYP3A4 moderate inhibitors</th>
<th>Reduce IVA dose to 1 tablet or 1 packet of oral granules <strong>once daily</strong> (half of normal dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>Erythromycin</td>
<td>Clofazimine</td>
<td>CYP3A4 moderate inhibitors</td>
<td>Reduce IVA dose to 1 tablet or 1 packet of oral granules <strong>once daily</strong> (half of normal dose)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Rifabutin</td>
<td>Phenobarbital</td>
<td>Phenotoin</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Grapefruit Juice</td>
<td>CYP3A4 moderate inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Lumacaftor/ivacaftor**
- Adults and pediatrics age ≥6 years: 2 tablets (LUM 200 mg/IVA 125 mg) every 12 hours
- Pediatric patients age 6 through 11 years: 2 tablets (LUM 100 mg/IVA 125 mg) every 12 hours
- Children age 2 to <6 years:
  - < 14 kg: 1 packet (LUM 100 mg/IVA 125 mg) every 12 hours
  - ≥ 14 kg: 1 packet (LUM 150 mg/IVA 188 mg) 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 50 mg/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: 2 tablets (ELX 100 mg/TEZ 50 mg/IVA 75 mg) in the morning and IVA 150 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.