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Class Update with New Drug Evaluation: Oral Cystic Fibrosis Modulators

Date of Review: July 2018
Generic Name: tezacaftor/ivacaftor

End Date of Literature Search: May 2018
Brand Name (Manufacturer): Symdeko™ (Vertex)
Dossier Received: yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this class update is to evaluate new evidence for the safety and effectiveness of oral cystic fibrosis (CF) modulators in reducing respiratory symptoms or pulmonary exacerbations associated with CF and improving quality of life as well as to evaluate the evidence and place in therapy of tezacaftor/ivacaftor (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:
Tezacaftor/ivacaftor:
- There is low quality evidence that TEZ/IVA modestly improves ppFEV$_1$ compared to placebo in patients with cystic fibrosis (CF) homozygous for the F508del mutation. Therapy has been shown to increase FEV$_1$ by a mean absolute change from baseline of 3.4% compared to -0.6% with placebo (mean difference of 4.0%).
- There is low quality evidence that TEZ/IVA decreases pulmonary exacerbations over 24 weeks compared to placebo (0.64 vs. 0.99 events per year; rate ratio 0.65; 95% CI 0.48 to 0.88) and improves quality of life with no impact on body mass index (BMI) in patients with CF homozygous for the F508del mutation.
- There is insufficient evidence that TEZ/IVA has a significant effect on clinically important outcomes (pulmonary exacerbations, hospitalizations, body mass index [BMI]) for the treatment of CF in those heterozygous for the F508del mutation and a second allele predicted to have residual function compared to

placebo over IVA monotherapy. Therapy was associated with a small statistical mean difference in $ppFEV_1$ compared to placebo (6.8%; 95% CI 5.7 to 7.8). However, this was estimated by averaging the change at weeks 4 and 8. There is insufficient evidence of a decrease in pulmonary exacerbations in this patient population.

- There is low quality evidence of a small, 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 and a second allele predicted to have residual function.
- TEZ/IVA has not demonstrated a significant effect in patients who are heterozygous for the F508del mutation and a second allele not predicted to be responsive to therapy and should not be used in this patient population.

Ivacaftor:

- There is low quality evidence that IVA improves percent predicted FEV_1 ($ppFEV_1$) compared to placebo (least square mean [LSM] difference 4.7%; 95% CI 3.7 to 5.8) and improves Cystic Fibrosis Questionnaire-revised (CFQ-R) respiratory domain score (0-100 scale) with 58% of patients in the IVA group achieving a 4 point or greater difference compared to 33% in the placebo group (ARR 25%; NNT 4), in patients heterozygous for the F508del mutation and a second allele with a CFTR mutation with residual function. This is based on one phase 3 randomized, 8-week crossover trial.[1] There was no significant difference seen in pulmonary exacerbations.
- There is insufficient evidence that IVA has a clinically relevant impact on outcomes of interest for recently approved CFTR mutations which were approved based on in vitro cell-based data only (E56K, S549R, K1060T, P67L, E193K, A1067T, R74W, L206W, G1069R, D110E, R347H, D579G, R1070Q, D1270N, D110H, R352Q, S945L, R1070W, G1349D, R117C, A455E, S977F, F1074L, F1052V, D1152H).

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 ($ppFEV_1$ <40%) or very mild CF ($ppFEV_1$ >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.

Previous Conclusions:

Ivacaftor:

- There is moderate quality evidence that ivacaftor (IVA) monotherapy is effective in patients with the G115D mutation. IVA has been shown to increase forced expiratory volume in one second [FEV_1] by an absolute value of 10.6% compared to placebo within 2 weeks of treatment; decrease number of patients with respiratory exacerbations at 24 weeks (OR 0.54; 95% CI 0.29 to 1.01) and increase weight by 2.7 kg.[2]
- There is insufficient evidence that IVA has a clinically relevant impact on outcomes of interest for other approved CFTR mutations. Studies either did not demonstrate a clinically significant effect (R117H), demonstrated a modest benefit in FEV_1 or sweat chloride only (G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R) or more recently, additional CFTR mutations were approved based on in vitro cell-based data only (E56K,S549R ,K1060T,

P67L,,E193K,A1067T, R74W , L206W , G1069R, D110E , R347H, D579G , R1070Q D1270N,D110H, R352Q, S945L, R1070W, G1349D, R117C, A455E , S977F, F1074L, F1052V, D1152H).

Lumacaftor/ivacaftor

- 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 FEV_1 (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.[3]
- LUM/IVA has not demonstrated a significant effect on FEV_1 in patients who are heterozygous for the F508del mutation and therapy should not be used in this patient population.

Recommendations:

- No changes recommended to the PDL.
- Continue to require modified prior authorization policy (**Appendix 3**) for the approval in appropriate patients.
- Remove the requirement of an FDA-approved CF gene mutation test from PA criteria (**Appendix 3**).
- Remove the requirement of baseline FEV_1 between 40% and 90% for approval of LUM/IVA from the PA criteria (**Appendix 3**).
- Add an acknowledgement in the PA criteria documenting that if therapy is approved, a referral will be made to case management (**Appendix 3**).

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.[4] Most available treatments for CF focus on symptom management and treatment of chronic infection, including antibiotics, dornase alfa, hypertonic saline, inhaled corticosteroids, oral nonsteroidal anti-inflammatory drugs, and inhaled bronchodilators.[5] CF is caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, found on the surface of cells in a variety of tissues where it functions as a regulator of the chloride ion channel.[6] Over 1900 mutations have been identified in the CFTR gene, with different protein defects resulting from the mutation.[7] 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. [7] 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.[8] 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, which accounts for approximately two thirds of the recognized mutations and carries the most severe prognosis.[9] 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.[1]

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.[10] According to National Institute of Clinical Excellence (NICE), an absolute change in $ppFEV_1$ of 5% or more would be considered clinically important.[10] 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.[11] 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.[12] 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%.[12] 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.[13] Weight 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.[13] 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 than40 mmol/L but patients with CF have elevated levels greater than 60 mmol/L.[12] 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.[7] Sweat chloride has been used as a biomarker for evaluation of change in CFTR activity in clinical trials of IVA.[14] 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. [12] 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.

IVA (Kalydeco®) and LUM/IVA (Orkambi®) are oral agents intended to enhance mutant CFTR protein function (**Table 1**).[14] Both of these agents are specific to CFTR mutation dysfunction. 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 1**).*[15]* The most common gating mutations, G551D and R117H, represent approximately 7% of the U.S. CF population. [14] 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.[2] However, while the 2-week endpoint was noted in a post-hoc analysis, the study was designed to look at outcomes at 24 weeks. 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.[16,17] IVA is designed to increase the time that activated CFTR channels at the cell surface remain open.[16,17]

LUM/IVA is a combination drug that contains the molecular entity LUM. 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 homozygous for the F508del mutation in the CFTR gene.[18] Phase 2 trials demonstrated lack of improvement in patients heterozygous for the F508del CFTR mutation.[19] It is currently FDA-approved for those age 12 years and older who are homozygous for the F508del mutation in the CFTR gene.[20] This patient group includes approximately 34% of the U.S. CF population.[14] 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 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 only went through 24 weeks. There is insufficient evidence to make the assumption that a reduction in pulmonary exacerbations is maintained as long as patients stayed 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.

Tezacaftor is a 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 two phase 3 randomized, double-blind trials in patients 12 years of age or older who were heterozygous for the F508del mutation and having a residual-function CFTR mutation as well as in those homozygous for F508del.[1,21]

Table 1: CFTR Modulators: Summary of Studied Mutations

CFTR Modulator	Mutation	Age Group Studied
IVA[15]	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	≥ 2 years
LUM/IVA[20]	F508del homozygous	≥ 6 years
Tezacaftor/IVA[1,21]	F508del homozygous F508del heterozygous + CFTR mutation with residual function	≥ 12 years

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), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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.

New Systematic Reviews:

No new high quality systematic reviews identified.

New Guidelines:

After review, one guideline was excluded due to poor quality.[22]

Additional Guidelines for Clinical Context:

Previous guidance from the National Institute for Health and Clinical Excellence (NICE) published recommendations for LUM-IVA for treating cystic fibrosis homozygous for the F508del mutation.[10] The following recommendation was included:

- *LUM/IVA is not recommended for treating CF in people 12 years and older who are homozygous for the F508del mutation in the CFTR gene.*

This recommendation came from a systematic review of the literature which identified 2 studies evaluating clinical effectiveness and safety of LUM/IVA. The panel concluded that the two trials were generally of good quality and included people with mild to moderate CF, and therefore, the clinical evidence may not be generalizable to people with severe CF ($ppFEV_1$ <40%) or with very mild CF ($ppFEV_1$ >90%). In addition, the absolute change in $ppFEV_1$ was less than 5% which would be considered clinically important, and there was insufficient long-term evidence to support the assumptions that a reduction in pulmonary exacerbations is maintained as long as people stay on treatment.

New Safety Alerts:
None identified.

New Formulations or Indications:

1. In September 2016, the FDA approved LUM/IVA for use in an expanded population of patients, children ages 6 through 11 years, who are homozygous for the F508del mutation.[20] This approval is expected to cover approximately 2,400 additional patients in the U.S. The efficacy in this group was extrapolated from previous studies in patients at least 12 years of age with additional pharmacokinetic analyses showing similar drug exposure levels.[19]

   The decision by the FDA to expand the age indication was also based on data from an open-label phase 3 safety study (n=58) in patients homozygous for the F508del CFTR mutation aged 6 through 11 years.[23] A baseline $ppFEV_1$ greater than 40% was required for inclusion. Efficacy endpoints, including sweat chloride, nutritional status, and quality of life were included as secondary outcomes. This study had many limitations and was not powered to evaluate efficacy outcomes. The study population generally had preserved lung function (mean $ppFEV_1$ 91.4%). A total of 11 patients (19.3%) had elevations in liver transaminases more than 3-times the upper-limit-of-normal (ULN) and 5 patients (8.8%) had elevations more than 5-times ULN.[23]The most common adverse events were cough, nasal congestion, pulmonary exacerbations and headache. There were no significant changes in $ppFEV_1$. There was a statistically significant decrease in sweat chloride from baseline (mean change -24.8 mmol/L; 95% CI -29.1 to -20.5) and 41/51 had a decrease of at least 15 mmol/L.[23] This decline in sweat chloride demonstrates a biochemical response to the drug but has not been associated with clinically meaningful efficacy outcomes.

   A randomized phase 3 trial evaluating nonclinical outcomes was published in July 2017 (**Table 2)**.[3] The primary outcome was mean change in lung clearance index ($LCI_{2.5}$) from baseline. LCI is used in trials with pediatric patients since studies among children with normal lung function with CF using normal spirometry have found LCI to be more sensitive than FEV_1 for detecting a response to treatment. LCI derived from a multiple breath washout provides a global measurement of ventilation inhomogeneity. It reflects abnormalities in ventilation in the respiratory tract compared to normal where changes are not easily detected with traditional pulmonary function techniques.[24] LCI has been shown to discriminate between individuals with CF and healthy, non-CF individuals. However, there is no evidence of a correlation between LCI and clinical outcomes including quality of life, pulmonary exacerbations or disease progression. Studies have demonstrated a significant, but variable correlation between LCI and FEV_1. While the gold standard

LCI uses sulfar hexafluoride, more centers are using a nitrogen-based washout which is more readily available.[24] However, the nitrogen washout technique has not yet been fully validated.

The baseline $LCI_{2.5}$ was 10.3 and baseline ppFEV_1 was 90%, demonstrating relatively preserved lung function. There were more patients in the treatment group with FEV_1 of less than 70% at baseline (10%) compared to placebo group (1%). There were also more subjects receiving inhaled antibiotics and inhaled corticosteroids in the placebo group compared to treatment group. There was a statistically significant difference between absolute improvement in LCI from baseline between the LUM/IVA group (LSM -1.01; 95% CI -1.27 to -0.75) compared to placebo (LSM 0.08; 95% CI -0.18 to 0.34). However, the upper and lower limits of the 2 confidence intervals are fairly close. The magnitude of effect is unclear but is much lower than what was seen with IVA in children with the G551D mutation (-2.07). This is the first study using LCI as the primary clinical outcome.
There was a significant change in baseline sweat chloride in both the LUM/IVA group and placebo group with a decrease from baseline of approximately 20 in both groups. Body mass index (BMI) significantly increased in both groups as well. There was no significant difference in quality of life as measured by the CFQ-R respiratory score and there was numerical improvement in both groups. There was no significant change in ppFEV1 in either group. [3] Infective pulmonary exacerbations were reported as a safety outcome and there was no significant difference between LUM/IVA and placebo (29% vs. 18%).

Vertex pharmaceuticals was involved in funding, study design, data collection analysis and interpretation as well as writing and publication of the manuscript.

There remains insufficient data in those with advanced lung disease. A phase 3b open-label study was conducted in those 12 years of age or older with advanced lung disease but remains unpublished (clinicaltrials.gov NCT02390219) and results are not available.

2. In May 2017, the FDA expanded the approved use of IVA for treating CF.[15] The new approval triples the number of rare gene mutations that IVA is approved for (**Table 1**). This expanded approval was based largely on laboratory data since many of these mutations are so rare. Approval was based on an in vitro cell-based model system designed to predict clinical response to IVA. When mutations responded to the lab test, data was extrapolated from earlier clinical trials in other mutations to support FDA approval. This expanded approval is expected to affect approximately 900 patients or 3% of the CF population. It is unknown how reliable in vitro data is to establish efficacy in these rare mutations. There is no evidence demonstrating efficacy in patients with these mutations.

3. In August 2017, IVA was approved for an additional 5 residual function mutations that result in a splicing defect in the CFTR gene increasing the number of approved mutations in the CFTR gene to 38. This approval was based on the EXPAND double-blind, randomized, crossover trial (**Table 3**) which evaluated the efficacy and safety of TEZ/IVA and IVA monotherapy in patients 12 years of age or older who were heterozygous for the F508del mutation and a second allele with a CFTR mutation with residual function. [1] Patients received two of the treatment arms for 8 weeks with an 8 week washout period between the treatment periods. The criteria for residual function mutation was an average sweat chloride of less than 86 mmol/L and incidence of pancreatic insufficiency of less than 50% or laboratory criteria (presence of mature CFTR and observed chloride transport). Results demonstrated a significant improvement in change in percent predicted FEV_1 with IVA compared to placebo (LSM 4.7%; 95% CI 3.7 to 5.8) and a significant improvement in the CFQ-R respiratory domain score with 58% of patients in the IVA group achieving a 4 point or greater difference compared to 33% in the placebo group (ARR 25%; NNT 4) with a high placebo response. However, there was only an absolute change from baseline in FEV_1 of 0.17 L in the IVA group. There was no significant difference in pulmonary exacerbations between IVA and placebo (rate ratio 0.46; 95% CI 0.21 to 1.01). There was no significant

difference in any outcomes between TEZ/IVA and IVA therapy and no clear benefit of the addition of TEZ in this patient population. Extensive exclusion criteria (anemia, abnormal liver function tests, colonization with certain organisms, concomitant CYP3A4 medications) limits generalizability to patients with more severe disease.

Randomized Controlled Trials:
A total of 12 citations were manually reviewed from the literature search. After manual review, 7 trials were excluded because of wrong study design (observational), outcome studied (non-clinical), wrong therapy (topical), or were published prior to November 2016. Two of the trials are included in the new drug evaluation. The remaining 3 trials are included below in **Table 2**.

Two of the trials supported expanded FDA approval of IVA and two trials studied the combination of tezacaftor/IVA. These studies will be further assessed for quality, risk of bias, and clinical significance in the following new drug evaluation.

Table 2: Characteristics of Included RCTs

Study	Comparison	Population	Primary Outcome	Results
Ratjen, et al.[3] Phase 3, RCT, DB	LUM 200mg / IVA 250 mg Q12 hours vs. matched placebo X 24 weeks	6-11 y/o, homozygous for the F508del mutation (n=206)	Lung clearance index 2.5 ($LCI_{2.5}$)	Mean absolute change in $LCI_{2.5}$ up to week 24: LUM/IVA: -1 Placebo: +0.1 P<0.0001
Rowe, et al.[25] Phase 2, DB RCT, PC	LUM/IVA vs. placebo X 56 days	18 years or older heterozygous for the F508del-CFTR mutation (n=126)	Absolute change in $ppFEV_1$ at day 56	Change from baseline in $ppFEV_1$ LUM/IVA: -0.6% Placebo: -1.2% LSM difference 0.6; 95% CI -1.7 to 2.9 >5% reduction $ppFEV_1$ LUM/IVA vs. placebo 22.6% vs. 14.3%; OR 1.7; 95% CI 0.7 to 4.3; p=0.25
Edgeworth, et al.[26] DB, PC, RCT, crossover	IVA vs. placebo	Adult patients with G551D CFTR mutation (n=20) *over 300 subjects did not meet eligibility criteria	Exercise tolerance (percentage change from baseline for maximal oxygen uptake; %VO2max)	There was no significant difference between IVA and placebo in %VO2max
Abbreviations: DB: double blind, FEV_1: forced expiratory volume in one second, IVA: ivacaftor; LUM: lumacaftor; PC: placebo controlled; RCT: randomized controlled trial; y/o = years old				

NEW DRUG EVALUATION: Tezacaftor/Ivacaftor

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

Clinical Efficacy:
Tezacaftor (TEZ) is a 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. [27] IVA 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. The combination of TEZ/IVA is FDA approved for patients with CF 12 years of age and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR that is responsive to TEZ/IVA based on in vitro data and/or clinical evidence.[27] The approval for mutations responsive based on in vitro data were allowed by the FDA for rare mutations that would be difficult to study. The intent of the assay was to determine if TEZ/IVA meets the threshold of increasing chloride transport by at least 10% from baseline. The FDA concluded that this threshold is reasonably likely to predict a clinical benefit with TEZ/IVA. However, this data does not show that TEZ offers additional benefit on top of IVA monotherapy.

TEZ/IVA was approved based on three phase 3 studies in three different CFTR mutation subpopulations (**Table 3**). The primary outcome in all trials was absolute change in percent predicted FEV_1 ($ppFEV_1$). Pulmonary exacerbations was a secondary endpoint and was defined as a new event or change in antibiotic therapy for any four or more of the following symptoms: change in sputum, hemoptysis, increased cough and/or dyspnea, malaise, fever, weight loss, sinus pain, sinus drainage, change in physical examination of the chest, decrease in pulmonary function by 10%, or radiographic changes.

Table 3: Clinical Studies Supporting Approval of Tezacaftor/IVA

Study	Follow-up Duration	CFTR mutation	Absolute change in percent predicted FEV1 compared to placebo (least-squares mean difference)
106 (EVOLVE)	24 weeks	Homozygous for the F508del mutation	4.0% (3.1 to 4.8)
108 (EXPAND)	8 weeks	Heterozygous for F508del mutation and a second allele with a CFTR mutation predicted to have residual CFTR function	6.8% (5.7 to 7.8)
107 (unpublished)	12 weeks	CF patients ≥ 12 years, heterozygous for F508del-CFTR mutation and 2nd CFTR mutation not likely to respond to TEZ and/or IVA therapy	1.2% (-0.3 to 2.6)

Study 106 is a fair quality trial that compared TEZ/IVA to placebo that demonstrated a small, but statistically significant improvement in absolute change in $ppFEV_1$ in those homozygous for the F508del mutation.[21] LUM/IVA previously demonstrated minimal efficacy in this population and is FDA approved. The absolute change in ppFEV1 was 3.4% (95% CI 2.7 to 4.0) and the difference compared to placebo was 4.0% (95% CI 3.1 to 4.8). This absolute change is modest with unknown clinical significance. This is slightly increased from what was observed in trials evaluating LUM/IVA (absolute change from baseline of 2.5%).

There was no significant difference in BMI between TEZ/IVA and placebo (< 1% increase from baseline). Lastly, there was a statistically significant decrease in pulmonary exacerbations with TEZ/IVA compared to placebo (RR 0.65; 95% CI 0.48 to 0.88) and an improvement in quality of life, as measured by the respiratory domain of the CFQ scale. The absolute change from baseline was 5 points in the treatment group, which is slightly higher than the minimally clinically important difference of 4 points. The number of pulmonary exacerbations requiring either intravenous (IV) antibiotics and/or hospitalizations was also lower in the TEZ/IVA group (RR 0.53; 95% CI 0.34 to 0.82) and was fairly low in both groups (0.54 per patient per year in TEZ/IVA and 0.29 per patient per year in placebo group). Since there was not an IVA arm in this trial, it is difficult to demonstrate the contribution of each component to the treatment. Extensive exclusion and inclusion criteria limits generalizability of the results. Exclusion criteria included those with any significant comorbidity left up to the discretion of the provider, limited subjects included with severe disease (FEV < 40%) or mild disease (FEV > 90%), and overall patients were generally young white adults from outside the U.S. Additionally, only approximately 20% of subjects were from the U.S.[21]

Study 108 is a poor-quality study that compared TEZ/IVA to IVA monotherapy and placebo in a 3-treatment crossover design study in subjects who are heterozygous for the F508del mutation and a second allele with a CF mutation predicted to have residual function (**Table 4**).[1] Neither IVA monotherapy or LUM/IVA have demonstrated improvement in lung function in this population. Each patient received two of the three interventions for eight weeks with an 8-week washout period in between. Criteria for including mutations were 1) having residual function based on population-level phenotypic data and 2) in vitro responsiveness to IVA. Overall, both TEZ/IVA and IVA monotherapy resulted in statistically significant improvements in $ppFEV_1$ (see evidence table). The difference between TEZ/IVA and IVA was modest, but also statistically significant (2.1%; 95% CI 1.2 to 2.9). [1] Both therapies also provided significantly better quality of life (CFQ-R respiratory domain) compared to placebo with no difference between the two treatment groups. Pulmonary exacerbations were an exploratory outcome only and there was no significant difference between either group and placebo. Concerns with this study include the short duration of treatment (8 weeks), the primary endpoint of absolute change in $ppFEV_1$ was calculated as an average of the four-week and eight-week measurements, and the study was not designed to detect differences in clinically important outcomes such as pulmonary exacerbations and BMI. Additionally, the crossover design may increase risk of blinding being broken or a carry-over effect in the results. There were a considerable amount of subjects who were not on standard of care with dornase alfa (~40%) and/or inhaled antibiotics (~70%). Additionally, to be included subjects had to have criteria for residual function defined as: either sweat chloride ≥ 60 mmol/L or evidence of chronic sinopulmonary disease. Lastly, not all of the individual mutations included clearly demonstrated an improvement in ppFEV1 with TEZ/IVA compared to IVA alone. However, the study was not powered to detect a difference at individual mutation level. [1]

Study 107 was a phase 3 randomized, double blind, placebo-controlled study which evaluated TEZ/IVA in subjects who are heterozygous for the F508del mutation and a second mutation predicted to be unresponsive to TEZ and/or IVA therapy over 12 weeks.[28] It is unpublished and cannot fully be assed for quality. Mutations that were unlikely to respond were identified by the following criteria: biological plausibility, clinical severity (average sweat chloride > 86 mmol/L), percentage of patients with pancreatic insufficiency, and in vitro testing. There was no significant difference in change from baseline in $ppFEV_1$ between TEZ/IVA and placebo (1.2%; 95% CI -0.3 to 2.6) and an overall change from baseline with treatment of 1.4%. There was no difference in any secondary endpoints (pulmonary exacerbations, quality of life or BMI) between the two groups demonstrating minimal efficacy in this patient population. [28]

Lastly, in vitro assay day was also used to support the use of TEZ/IVA in certain rare CFTR mutations. The FDA determined that an in vitro assay response above a certain threshold may be reasonably predictive of a clinical benefit. However, this data does not predict the magnitude of benefit that may be observed or not observed with therapy and more clinical data is needed before TEZ/IVA can be recommended in additional patient populations with CF.

Further data is needed to better assess efficacy of TEZ/IVA. Evidence remains insufficient to determine the effects of TEZ/IVA on long term disease progression or to know if TEZ/IVA is effective in patients with very severe CF ($ppFEV_1$ <40%) or very mild CF ($ppFEV_1$ >90%). Additionally, evidence remains insufficient to determine comparative efficacy of TEZ/IVA and LUM/IVA (LUM/IVA) or against other standard of care including dornase alfa and hypertonic saline.

Table 4: Second allele in patients heterozygous for the F50ddel CF mutation included for TEZ/IVA FDA Approval[28]

***CFTR* Mutations Predicted to Have Residual Function and That May Be Responsive to Ivacaftor**			
2789+5G→A	R74W	R352Q	R1070W
3849+10kbC→T	D110E	A455E	F1074L
3272-26A→G	D110H	D579G	D1152H
711+3A→G	R117C	S945L	D1270N
E56K	E193K	S977F	
P67L	L206W	F1052V	
E831X	R347H	K1060T	

Clinical Safety:

The most common side effects observed in clinical trials evaluating TEZ/IVA that occurred in a greater number of TEZ/IVA-treated patients than placebo-treated patients include headache, nausea, sinus congestion and dizziness (**Table 5**). Headache and nausea were the most common, but rates were only slightly higher than placebo. Serious adverse reactions that occurred more frequently than placebo included distal intestinal obstruction syndrome (3 patients [0.6%] vs. 0 patients for TEZ/IVA and placebo, respectively). [27] Overall discontinuations due to adverse reactions was low in clinical trials (1.6%) and comparable to placebo (2.0%).There were no reported deaths in trials.[27]

Table 5: Adverse Drug Reactions Which Occurred More Commonly in TEZ/IVA-Treated Patients Than Placebo-Treated Patients

Adverse Reactions	TEZ/IVA (n=334) N (%)	Placebo (n=343) N (%)
Headache	49 (15)	44 (13)
Nausea	29 (9)	24 (7)
Sinus congestion	13 (4)	6 (2)
Dizziness	12 (4)	8 (2)

Additional safety concerns that need to be monitored for include elevated transaminase levels and drug-drug interactions mediated through CYP3A4.[27] Transaminases are recommended to be assessed prior to treatment, every 3 months for the first year of treatment, and yearly afterward.[27] Since both TEZ and IVA are substrates of CYP3A4, concomitant use of strong CYP3A4 inducers may decrease TEZ/IVA efficacy and is not recommended.[27]

Several unanswered safety questions exist as TEZ/IVA was studied in a relatively small number of patients in clinical trials. There is insufficient information of safety data in very severe CF, very mild CF, or patients with significant comorbidities as these patients were not included in the clinical trials. Additionally, there is insufficient information to determine long-term safety of TEZ/IVA as clinical trial data is limited to 24 weeks.

Table 6. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	TEZ is a 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. IVA 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	Exposure 3 times higher when administered with fat-containing foods compared to a fasting state
Distribution and Protein Binding	TEZ 99% protein bound; IVA 99% protein bound
Elimination	TEZ: 72% eliminated through feces, 14% in urine; IVA: 88% eliminated through feces, minimal urine excretion
Half-Life	TEZ: 29 hours; IVA: 20 hours
Metabolism	CYP3A4

Abbreviations: CFTR: cystic fibrosis transmembrane conductance regulator, IVA: ivacaftor, TEZ: tezacaftor

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Quality of life
2) Hospitalizations
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 to week 24 (study 106) or to the average of week 4 and week 8 (study 108)

Table 7. 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. Taylor-Cousar, et al. [21] Phase 3, RCT, DB, PC, PG Study 106	1. Tezacaftor 100 mg daily + IVA 150 mg twice daily 2. matched placebo	Demographics: • Mean FEV_1: 60% • Mean age: 26 yr • Concomitant hypertonic saline: 51% • Concomitant dornase alfa: 70% Key Inclusion Criteria:	ITT: 1. 251 2. 259 PP: 1. 235 2. 240 Attrition:	Primary Endpoint: Absolute change in percent predicted FEV_1 1. 3.4% 2. -0.6% LSM difference 4.0%; 95% CI 3.1 to 4.8; p<0.001	NA	Discontinuations due to AE: 1. 7 (2.8%) 2. 8 (3.1%) 95% CI & p-value NR Serious AE:	NA	**Risk of Bias (low/high/unclear)**: low Selection Bias: low; randomized with an interactive web response system, baseline characteristics similar but more patients in the placebo group were on standard therapies than in the treatment group (dornase alfa (72% vs. 66.5%), inhaled antibiotic (62.5% vs. 54.8%), and inhaled corticosteroids (63% vs. 56%))

EVOLVE	x 24 weeks	• ≥12 y/o • Homozygous for F508del mutation • FEV1 ≥ 40% and ≤ 90% • Stable CF disease. Key Exclusion Criteria: • Significant comorbidity • Risk factors for torsades de pointes • Hg < 10 g/dl • Abnormal liver function • GFR≤ 50 ml/min • Respiratory infection or CF exacerbation in previous 4 weeks • Colonization with *Burkholderia or Mycobacterium* • Alcohol or drug abuse in past year • Use of mod-strong inhibitors or inducers of CYP3A4	1. 16 2. 18	Secondary Endpoints: Total Number of Pulmonary Exacerbations through week 24 (annuazed rate) 1. 78 (0.64 events per year) 2. 122 (0.99 events per year) Rate ratio vs. placebo: 0.65; 95% CI 0.48 to 0.88; p=0.005 Percent of patients with an increase in the CFQ-R respiratory domain score of at least 4 points: 1. 51.5% 2. 35.7% OR 2.17; 95% CI 1.47 to 3.21 p-value NR	NA 16%/7	1. 31 (12.4%) 2.47 (18.2%) 95% CI & p-value NR	NA	Performance Bias: low; subjects and investigator blinded, double-dummy design Detection Bias: low; site monitor and study team blinded Attrition Bias: low; FAS (1. 248, 2. 256) used for efficacy analysis (all randomization patients who took 1 dose of study drug), low overall attrition and similar between groups Reporting Bias: high; funded by Vertex Pharmaceuticals. Vertex designed the protocol, analyzed the data. **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 < 40%) or with FEV > 90%, patients generally young white adults from outside the U.S. and a significant number of patients not on standard of care therapies Intervention: N/A Comparator: Lack of IVA arm makes it difficult to determine effect of each component 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: Multinational in 91 sites in the United States, Canada, and Europe (75% Europe)
2. Rowe, et al.[1] Phase 3, RCT, PC, DB, crossover design Study 108 EXPAND	1. tezacaftor 100 mg + IVA 150 mg BID 2. IVA 150 mg BID 3. placebo Subjects received 2 8-week treatment regimens with a washout	Demographics: • Baseline ppFEV1: 62% • Mean age: 34.8 yr • Class V noncanonical splice mutation: 60% • Class II to IV residual function mutations in the second allele: 40% • Concomitant dornase alfa: 61% • Concomitant hypertonic saline: 48% Key Inclusion Criteria: • ≥12 y/o • Heterozygous for F508del mutation and a	ITT: 1. 162 2. 157 3. 162 PP: 1. 160 2.157 3. 162 Attrition: 1. 2 2. 2 3. 6	Primary Endpoint: Absolute change in ppFEV$_1$ from baseline to the average of week 4 and 8 1. 6.5% 2. 4.4% 3. -0.3% *IVA vs. placebo:* LSM 4.7; 95% CI 3.7 to 5.8 P<0.001 *TEZ/IVA vs. placebo* LSM 6.8; 95% CI 5.7 to 7.8 P<0.001 *TEZ/IVA vs. IVA*	NA NA	Outcome: Discontinuations due to AE: 1. 0 (0%) 2. 2 (1%) 3. 1 (<1%) Severe AE (grade 3 or 4): 1. 4 (2%) 2. 8 (5%) 3. 9 (6%)	NA NA	**Risk of Bias (low/high/unclear)**: unclear Selection Bias: low; randomized to 1 of 6 treatment sequences** including 2 of the treatment regimens with an interactive web response system, baseline characteristics similar Performance Bias: low; subjects and investigator blinded, double-dummy design Detection Bias: low; site monitor and study team blinded, crossover design Attrition Bias: unclear; FAS used for efficacy analysis (all randomization patients who took 1 dose of study drug), low overall attrition (5%), but some variability between groups (10% in the group randomized to placebo first) Reporting Bias: high; funded by Vertex Pharmaceuticals. Vertex designed the protocol, analyzed the data.

	period of 8 weeks in between**	second allele with a CFTR mutation predicted to have residual CFTR function • FEV_1 ≥ 40% and ≤ 90% • Stable CF disease • Sweat chloride ≥ 60 mmol/L or evidence of chronic sinopulmonary disease* <u>Key Exclusion Criteria</u>: • See EVOLVE above		LSM 2.1; 95% CI 1.2 to 2.9 P<0.001 <u>Secondary Endpoints</u>: <u>Percent of patients with an increase in the CFQ-R respiratory domain score of at least 4 points:</u> 1. 105 (65%) 2. 91 (58%) 3. 53 (33%) *IVA vs. placebo:* 95% CI & p-value NR *TEZ/IVA vs. placebo* 95% CI & p-value NR *TEZ/IVA vs. IVA* 95% CI & p-value NR <u>Exploratory Outcome:</u> <u>Pulmonary Exacerbations:</u> 1. 11 (0.34 events per year) 2. 9 (0.29 events per year) 3. 20 (0.63 events per year) *IVA vs. placebo (rate ratio)* RR 0.46; 95% CI 0.21 to 1.01 P-value NR *TEZ/IVA vs. placebo:* RR 0.54; 95% CI 0.26 to 1.13 P-value NR *TEZ/IVA vs. IVA:* RR 1.18; 95% CI 0.49 to 2.87 P-value NR	NA NA NA NA NA NA NA			**Applicability**: <u>Patient</u>: Extensive exclusion and inclusion criteria limits generalizability including significant comorbidity left up to the discretion of the provider, limited subjects included with severe disease (FEV < 40%) or with FEV > 90%, patients generally young white adults from outside the U.S. <u>Intervention</u>: Crossover trial design increases risk of a "carry over" treatment effect <u>Comparator</u>: Unclear on appropriateness of IVA as a comparator since it was found to be not effective in those homozygous for F508del <u>Outcomes</u>: The 8 week outcomes were actually an average of the 4 week and 8 week measurements, pulmonary exacerbations was an exploratory outcome. 8 weeks is not long enough follow-up to evaluate clinically important outcomes. <u>Setting</u>: Multinational including sites in North America (~50%) and Europe

<u>Abbreviations</u> [alphabetical order]: AE = adverse events; ARR = absolute risk reduction; BID = twice daily; CI = confidence interval; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; CV = cardiovascular; DB = double blind; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; GFR = glomerular filtration rate; ITT = intention to treat; HTN = hypertension; IVA = IVA; LSM = least squares mean difference; 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; RCT = randomized controlled trial; yr = year

*Manifested by at least 1 of the following: persistent colonization/infection with typical CF pathogens, chronic cough and sputum production, persistent chest abnormalities, nasal polyps or chronic sinusitis

**Sequence 1: TEZ/IVA - washout – IVA; Sequence 2: IVA – washout – TEZ/IVA; Sequence 3: TEZ/IVA – washout – placebo; Sequence 4: placebo – washout – TEZ/IVA; Sequence 5: IVA – washout – placebo; Sequence 6: placebo – washout - IVA

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	GRAN PACK	KALYDECO	IVA	N
ORAL	TABLET	KALYDECO	IVA	N
ORAL	TABLET	ORKAMBI	LUM/IVA	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November week 4, 2017
1 IVA.mp. 337
2 LUM.mp. 137
3 kalydeco.mp. 22
4. Cystic Fibrosis Trtansmembrane Conductance Regulator/ 8792
5 orkambi.mp. 16
6. 1 or 2 or 3 or 4 or 5
7. cystic fibrosis.mp or Cystic Fibrosis/ 26187
8 6 and 7
9 limit 8 to (English language and humans and yr="2015-Current" and (clinical trial or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews)) 12

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®)

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/

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. What diagnosis is being treated?	Record ICD10 code. Go to #3	
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. 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 #5	

Approval Criteria		
5. Is the request for ivacaftor?	**Yes:** Go to #6	**No:** Go to #10
6. What is the patient's baseline sweat chloride level?	Prescriber must provide documentation before approval. Document baseline value. Go to #7	
7. Does the patient have a diagnosis of cystic fibrosis and is 2 years of age or older?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have a documented mutation in the CFTR gene that ivacaftor is FDA approved for (see below)? FDA approved CFTR mutations include: 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	**Yes:** Go to #17	**No:** Go to #9 If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).

Approval Criteria		
9. 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:** 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. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).
10. Is the request for lumacaftor/ivacaftor?	**Yes:** Go to #11	**No:** Go to #13
11. Does the patient have a diagnosis of cystic fibrosis and is 6 years of age or older?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Does the patient have a documented homozygous Phe508del mutation in the CFTR gene detected by an CF mutation test?	**Yes:** If the patient is younger than 12 years of age, refer case to OHP Medical Director; otherwise, Go to #17	**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. CF due to other CFTR gene mutations are not approved indications (including those who are heterozygous for the F508del mutation)
13. Is the request for tezacaftor/ivacaftor?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
14. Does the patient have a diagnosis of cystic fibrosis and is 12 years of age or older?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness
15. Does the patient have a documented homozygous Phe508del mutation in the CFTR gene detected by a CF mutation test?	**Yes:** Go to #17	**No:** Go to #16 If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use.
16. Does the patient have at least one mutation that is responsive to tezacaftor/ivacaftor based on in vitro data and FDA labeling? Note: A list of CFTR gene mutations that produce CFTR protein and are responsive to tezacaftor/ivacaftor include: 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	**Yes:** Go to #17	**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.
17. 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 #18	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
18. Is the patient on concomitant therapy with a strong CYP3A4 inducer (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #19
19. What are the baseline liver function (AST/ALT) and bilirubin levels (within previous 3 months)?	Document labs. Go to #20 If unknown, these labs need to be collected prior to approval.	
20. 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

Renewal Criteria		
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
3. If the prescription is for lumacaftor/ivacaftor or 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)

Renewal Criteria		
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 2 to <6 years:
  - < 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 2 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 Grapefruit Juice	CYP3A4 strong inducers	Concurrent use is **NOT** recommended

<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
- Hepatic impairment
    - Moderate impairment (Child-Pugh class B):
        - 2 tablets in the morning and 1 tablet in the evening
    - Severe impairment (Child-Pugh class C): Use with caution at a dose of 1 tablet twice daily, or less, after weighing the risks and benefits of treatment.
- 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 ≥12 years: 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning and IVA 150 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: *7/18 (MH); 11/16; 11/15; 7/15; 5/15; 5/14; 6/12*
Implementation: *8/15/18; 1/1/16; 8/25/15; 8/12*