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Class Update: Oral Cystic Fibrosis Modulators

Date of Review: November 2016 **Date of Last Review:** November 2015

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. Additionally, the purpose is to identify who will benefit from oral CF modulators and to better define a clinical response to treatment.

Research Questions:
1. What is the comparative evidence for oral CF modulators (ivacaftor and lumacaftor/ivacaftor) in improving clinically important outcomes such as respiratory symptoms, pulmonary exacerbations, 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 ivacaftor or lumacaftor/ivacaftor?
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 ivacaftor or lumacaftor/ivacaftor?
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:
- Evidence remains insufficient to compare the efficacy/effectiveness or safety of ivacaftor and lumacaftor/ivacaftor for the treatment of children or adults with CF.
- Evidence remains insufficient to determine the long term effects of ivacaftor and lumacaftor/ivacaftor on long term disease progression.
- Evidence remains insufficient to determine appropriate criteria for stopping ivacaftor or lumacaftor/ivacaftor for lack of effectiveness.
- Evidence remains insufficient to know if lumacaftor/ivacaftor is effective in patients with very severe CF ($ppFEV_1$ <40%) or very mild CF ($ppFEV_1$ >90%).
- Evidence remains insufficient to support clinically important changes in $ppFEV_1$ with lumacaftor/ivacaftor; in addition, there is insufficient long-term evidence to support any improvement in clinically meaningful outcomes with lumacaftor/ivacaftor (i.e., mortality, frequency of pulmonary exacerbations, quality of life and respiratory symptoms).
- Evidence remains insufficient to suggest ivacaftor reduces pulmonary exacerbations or significantly improves lung function in patients with the *R117H* mutation

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- Evidence remains insufficient to support improvements in clinically meaningful outcomes with ivacaftor in the FDA approved gating mutations other than G551D (G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P and G1349D). Evidence of benefit is limited to a modest improvement in FEV_1 compared to placebo and an improvement in sweat chloride concentrations. However, there is no evidence that sweat chloride is correlated with meaningful clinical benefits.
- There is insufficient evidence that lumacaftor/ivacaftor is effective or safe and well tolerated over 24 weeks in children ages 6 to 11 years homozygous for the *F508del* mutation in the CFTR mutation. The FDA approved this expanded indication based on pharmacokinetic data and safety data from an open-label phase 3 safety study (n=58) including only short- term $ppFEV_1$ results.

Recommendations:

- No changes recommended to the PDL.
- Continue to require prior authorization policy (Appendix 3) for the approval in appropriate patients. Amend criteria to require approval from the OHP Medical Director for use of Orkambi (lumacaftor/ivacaftor) in children ages 6 through 11 years.

Previous Conclusions:

- Treatment with LUM/IVA is approved for patients with CF homozygous for the F508del mutation in the CFTR gene. Lifelong therapy is used to slow lung function decline. Treatment has not been demonstrated to be curative.
- There is moderate quality evidence from two randomized controlled trials (RCTs) that short-term use of LUM/IVA 400/250 mg twice daily improves percent-predicted FEV1 compared to placebo over 24 weeks (mean difference 2.8% to 3.3% with LUM 400 mg/IVA twice daily and LUM 600 mg/IVA twice daily, respectively) in CF patients homozygous for the F508del mutation in the CFTR gene; however, the clinical significance of this improvement is unknown. The magnitude of effect (2.8%) was considerably less than that produced by IVA alone versus placebo in patients with G115D mutation (11%) at 24 weeks, and similar to that for IVA alone in the F508del mutation for which IVA was decided to be not efficacious. There is insufficient and inconsistent evidence that LUM/IVA improves body mass index (BMI). Changes in the quality of life questionnaire (CFQ-R respiratory domain) and pulmonary exacerbations were not statistically significant compared to placebo due to hierarchal design, but there was a nominal decrease in pulmonary exacerbations (LUM 400 mg RR 0.61; 95% CI 0.49 to 0.76 for and LUM 600 mg RR 0.70; 95% CI 0.56 to 0.87), and was confounded by other concomitant pre-modulation therapies.
- An area of clinical uncertainty remains whether the combination of LUM/IVA provides more benefit than IVA monotherapy which was found to be deleterious in F508del homozygotes adults in previous clinical trials. With phase 2 trials demonstrating a dose dependent decrease in $PPFEV_1$ with LUM alone, LUM/IVA treatment effect similar to IVA monotherapy, and LUM monotherapy not included as a comparator in confirmatory studies, the clinical significance of the combination agent remains uncertain.
- It is unclear from existing data whether the LUM/IVA combination is superior to IVA alone; evidence so far is insufficient to support use of IVA monotherapy in patients homozygous for the F508del mutation as the drug did not significantly improve percent-predicted FEV1. Although statistically significant, the small FEV1 effect seen with LUM/IVA in CF patients homozygous for the F508del mutation was similar to that for IVA alone (2-3%). The individual components of the drug were not included in phase 3 studies, so it is unknown to what degree each medication contributes to its efficacy.
- There is low quality evidence that LUM/IVA produces a numerical decrease in sweat chloride of about 10 mmol/L, which is a much smaller decrease compared to that observed with IVA alone in patients with the G551D and R117H mutations (50 and 24 mmol/L, respectively). However, change in sweat chloride is not known to be clinically relevant to decline in respiratory function.
- Minor and reversible elevations of transaminases were seen across all groups and significant elevations occurred only in 5.1% of placebo patients and 5.2% of LUM/IVA patients. Serious adverse events related to abnormal liver function were not observed in the placebo group and were reported for seven

patients in the LUM/IVA groups. Due to hepatic and respiratory related safety concerns, transaminases and pulmonary function should be monitored throughout therapy; this is particularly important in pediatric patients receiving therapy who will be potentially receiving therapy for years to come.

- LUM/IVA did not demonstrate a significant effect in patients who were heterozygous for the F508del mutation and therapy should not be used in patient populations outside of those homozygous for the F508del mutation.
- More data are needed to determine the long-term effects of LUM/IVA on survival and quality of life as well as the applicability of LUM/IVA in real-world settings, including criteria that define treatment success and time to response after initiation.

Previous Recommendations:

- Maintain LUM/IVA as non-preferred and update PA criteria. Continue to monitor for patient adherence and adopt clinical criteria as needed to adequately assess clinical response as further data become available.

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.[1] 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.[2] 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.[3] Over 1900 mutations have been identified in the CFTR gene, with different protein defects resulting from the mutation.[4] 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.[4] 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.[5] 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.[6]

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 because of the heterogeneous nature of the condition.[7] 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.[8] 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.[9] 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.[9] 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 <40 mmol/L but patients with CF have elevated levels >60 mmol/L.[10] 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.[4] Sweat chloride has been used as a biomarker for evaluation of change in CFTR activity in clinical trials of ivacaftor.[11] 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. [10] 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.

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Ivacaftor (Kalydeco®) and lumacaftor/ivacaftor (Orkambi®) are oral agents intended to enhance mutant CFTR protein function.[12] Both of these agents are specific to CFTR mutation dysfunction. Ivacaftor is a CFTR potentiator indicated for the management of CF in patients in patients 2 years of age and older who have one of the following gating mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H.*[13] The most common gating mutations, G551D and R117H, represent approximately 7% of the U.S. CF population.[12] In trials of patients with the G115D mutation, ivacaftor 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.[14] However, the 2-week endpoint was noted in a post-hoc analysis but the study was designed to look at outcomes at 24 weeks. Ivacaftor 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.[15,16] Ivacaftor is designed to increase the time that activated CFTR channels at the cell surface remain open. [15,16]

Lumacaftor/ivacaftor is a combination drug that contains the molecular entity lumacaftor. The exact mechanism of lumacaftor 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 ivacaftor 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.[17] Phase 2 trials demonstrated lack of improvement in patients heterozygous for the F508del CFTR mutation.[18] It is currently FDA-approved for those age 12 years and older who are homozygous for the F508del mutation in the CFTR gene.[19] This patient group includes approximately 34% of the U.S. CF population.[12] Studies of lumacaftor/ivacaftor did not demonstrate clinically significant results on meaningful outcomes. It was associated with only a absolute 2.8% improvement in FEV1 (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 people stayed on treatment. It remains unclear if the combination provides more benefit than ivacaftor alone which was found to be deleterious in F508del homozygous adults in previous trials.

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:

A Cochrane Collaboration systematic review evaluated the effects of CFTR potentiators on clinically important outcomes in children and adults with CF.[20] Four RCTs were identified and included in the review (n=378) comparing ivacaftor to placebo. No trials including lumacaftor/ivacaftor were included in this analysis.

Risk of bias in included trials was moderate. Participant blinding was not clear and participant data were excluded from the analysis in 3 trials. Overall, in the adult phase 3 trial, there was an improvement in relative change from baseline in FEV_1 at 24 weeks (mean difference 16.9%; 95% CI 13.6 to 20.2%) and 48 weeks (mean difference 16.80%; 95% CI 13.50 to 20.10%). In the pediatric trial, there was an improvement also seen at 24 weeks (mean difference 17.4%).[20] Results are not available out to 48 weeks in children and only interim data was available from a conference abstract. Significantly higher quality of life scores in the respiratory domain were reported in the adult trials, but not in the pediatric trials. No improvements in quality of life or lung function were reported in the F508del participants. In the phase 3 G551D trials, fewer participants developed pulmonary exacerbations when on ivacaftor than placebo (OR 0.54; 95% CI 0.29 to 1.01). Data reviewed were limited only to those with the G551D mutation. The authors concluded that in this population, phase 3 trials demonstrated a clinically relevant impact of ivacaftor on outcomes. [20]

New Guidelines:

1. Guidance from the National Institute for Health and Clinical Excellence (NICE) published recommendations for lumacaftor-ivacaftor for treating cystic fibrosis homozygous for the F508del mutation.[7] The following recommendation was included:
    - *Lumacaftor/ivacaftor 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 lumacaftor/ivacaftor. 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.

2. The CF Foundation developed clinical care guidelines for preschool-aged children with CF.[21] The guideline committee consisted of 16 CF pediatric experts and parents; however, non-specialists or experts in methodology were not included on the guideline committee. Overall, there are very little data in children ages 2 to 5 years old and therefore the recommendations included in the guideline are based on expert opinion and are likely to change based on additional research.

New Safety Alerts:

None identified.

New Formulations or Indications:

In September 2016, the FDA approved lumacaftor/ivacaftor for use in an expanded population of patients, children ages 6 through 11 years, who are homozygous for the F508del mutation.[19] 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' aged 12 years and older 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.[22] A baseline $ppFEV_1$ >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. [22] 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. [22] This decline in sweat chloride demonstrates a biochemical response to the drug but has not been associated with clinically meaningful efficacy outcomes.

Randomized Controlled Trials:

A total of 20 citations were manually reviewed from the literature search. After manual review, all 20 trials were excluded because of wrong study design (observational), outcome studied (non-clinical), wrong therapy (topical), or were published prior to November 2015.

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	GRAN PACK	KALYDECO	IVACAFTOR	N
ORAL	TABLET	KALYDECO	IVACAFTOR	N
ORAL	TABLET	ORKAMBI	LUMACAFTOR/IVACAFTOR	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to September Week 2, 2016
1 ivacaftor.mp. 212
2 lumacaftor.mp. 72
3 kalydeco.mp. 12
4. Cystic Fibrosis Trtansmembrane Conductance Regulator/ 6727
5 orkambi.mp. 2
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)) 20

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®)

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 or lumacaftor/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 G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene detected by an FDA-cleared CF mutation test?	**Yes:** Go to #14	**No:** Go to #9 If unknown, there needs to be a FDA-approved 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. Does the patient have a documented R117H mutation in the CFTR gene detected by an FDA-cleared 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 FDA-approved 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		
10. Is the request for lumacaftor/ivacaftor?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
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 FDA-approved CF mutation test?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness If unknown, there needs to be a FDA-approved 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 a baseline FEV1 is provided and is between ≥40% and ≤90% of predicted normal for age, sex and height for those ≥12 years of age and at least 40% for children ages 6 through 11 years?	**Yes:** If the patient is younger than 12 years of age, refer case to OHP Medical Director; otherwise, Go to #14	**No:** Pass to RPh. Deny; medical appropriateness If no baseline, request a baseline value before approving therapy.
14. 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 #15	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
15. Is the patient on concomitant therapy with a strong CYP3A4 inducer (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #16
16. What are the baseline liver function (AST/ALT) and bilirubin levels (within previous 3 months)?	Document labs. Go to #17	
17. 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 ivacaftor (see **Renewal Criteria**)	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is this the first time the patient is requesting a renewal (after 90 days of initial approval)?	**Yes:** Go to #2	**No:** Go to #4
2. If prescription is for ivacaftor: Does the patient have a documented physiological response to therapy and evidence of adherence after 30 days of treatment, as defined by a sweat chloride test that has decreased by at least 20 mmol/L from baseline?	**Yes:** Go to #7	**No:** Go to #3 Consider patient's adherence to therapy and repeat test in 2 weeks to 45 days to allow for variability in test. If sodium chloride has still not decreased by 20 mmol/L, deny therapy for medical appropriateness

Renewal Criteria		
3. If the prescription is for lumacaftor/ivacaftor: Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?	**Yes:** Go to #7	**No:** Pass to RPh; Deny (medical appropriateness)
4. Does the patient have documented response to therapy as defined as below : For patients age ≥6 years: • An improvement or lack of decline in lung function as measured by the FEV1 when the patient is clinically stable; OR • A reduction in the incidence of pulmonary exacerbations; OR • A significant improvement in BMI by 10% from baseline? For patients age 2-5 years (cannot complete lung function tests) • Significant improvement in BMI by 10% from baseline; OR • Improvement in exacerbation frequency or severity; OR • Sweat chloride test has decreased from baseline by 20 mmol/L from baseline?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient been compliant with therapy, as determined by refill claims history?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
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.	
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:

<u>Ivacaftor:</u>

- 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 ivacaftor	Co-administered drug category	Recommended dosage adjustment for ivacaftor
Ketoconazole Itraconazole Posaconazole Voriconazole Clarithromycin Telithromycin	CYP3A4 strong inhibitors	Reduce ivacaftor 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 ivacaftor 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 (lumacaftor 200 mg/ivacaftor 125 mg) every 12 hours
- Pediatric patients age 6 through 11 years: 2 tablets (lumacaftor 100mg/ivacaftor 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.

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