Drug Use Research & Management Program
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New Drug Evaluation: Lumacaftor/Ivacaftor

Date of Review: November 2015
Generic Name: Lumacaftor/Ivacaftor
PDL Class: Cystic Fibrosis Medications

End Date of Literature Search: September 2015
Brand Name (Manufacturer): Orkambi® (Vertex)
Dossier Received: Yes

Research Questions:

1. Is there evidence that lumacaftor/ivacaftor (LUM/IVA) improves clinically relevant outcomes in patients with cystic fibrosis (CF) homozygous for the F508del mutation in the CF transmembrane conductance regulator (CFTR) gene, including lung function, quality of life, frequency of pulmonary exacerbations, hospitalizations, and mortality with a clinically significant magnitude of benefit?
2. Is there evidence that LUM/IVA is safe in patients with CF homozygous for the F508del mutation in the CFTR gene?
3. Are there any additional mutations in which LUM/IVA has safely demonstrated efficacy?

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;[1] 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, [2] and similar to that for IVA alone in the F508del mutation for which IVA was decided to be not efficacious.[3] There is insufficient and inconsistent evidence that LUM/IVA improves body mass index (BMI).[1] 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. [1]
- 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.[3] 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.[3] 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%).[1,3] 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.

Recommendations:

- Maintain LUM/IVA as non-preferred and update PA criteria as presented in Appendix 3. 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.[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] Important outcomes for treatment include reduction in mortality, frequency of pulmonary exacerbations, and respiratory symptoms. Forced expiratory volume in one second (FEV_1) is a commonly used outcome in clinical trials. 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.[6] 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 in children with CF. [6] 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.[7] More recently, endpoints such as sweat chloride, nasal potential difference, and the intestinal current measurement are proposed surrogate markers of CFTR function, as these reflect sodium absorption and chloride secretion dependent on CFTR function.[8] Sweat chloride has been used as a biomarker for evaluation of change in CFTR activity in clinical trials of ivacaftor.[9] 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. [7] 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.

CF is caused by mutations in the CFTR gene, found on the surface of cells in a variety of tissues where it functions as a regulator of chloride ion channel.[10] Over 1900 mutations have been identified in the CFTR gene, with different protein defects resulting from the mutation.[8] The F508del mutation results in

misprocessing of CFTR resulting in failure of CFTR to travel to the cell surface, while the G551D and other gating mutations result in failure of CFTR to open channels at the cell surface. Lastly, the R117H mutation affects chloride conductance in the pore region of the channel leading to poor conductance of chloride ion.[8] There are three common alleles at the poly-T locus of the *R117H* gene (5T, 7T, 9T), with the 5T variant associated with greater severity of CF.[11] 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. .[3]

Ivacaftor is a potentiator of CFTR and is indicated for the management of CF in patients in patients 2 years of age and older who have one of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H.* [2,12–14] Compared to placebo, the effects of IVA demonstrated in trials of the G115D mutation were an 10.6% absolute increase in FEV1 which was seen 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.[2] However the two-week endpoint was noted in post hoc analysis; the study design aimed 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] The FDA recently approved LUM/IVA, a combination drug that contains a new 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.[3] However, the combination of LUM/IVA was approved after phase III trials demonstrated it had efficacy for the management of CF in patients 12 years of age and older homozygous for the F508del mutation in the CFTR gene.[1] Phase II trials demonstrated lack of improvement in patients heterozygous for the F508del CFTR mutation.[17]

Worsening of liver function has been reported and use of LUM/IVC should be used in caution in patients with advanced liver disease. Liver enzymes should be monitored prior to therapy, every 3 months during the first year of treatment, and annually thereafter.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning 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:

Approval of LUM/IVA was based on 2 Phase III, randomized, double-blinded, placebo-controlled trials (TRAFFIC AND TRANSPORT) that compared LUM/IVA to placebo over 24 weeks (n=1122) in patients with CF who were homozygous for the F508del CFTR mutation.[1] Each trial had three parallel arms: lumacaftor 600 mg once daily/ivacaftor 250 mg twice daily, lumacaftor 400 mg/ivacaftor 250 mg twice daily, and placebo twice daily. The trials had identical designs with the exception of ambulatory electrocardiography in TRAFFIC, and adolescent pharmacokinetic assessments in TRANSPORT. The primary endpoint was an absolute change in percent-predicted FEV1 ($PPFEV_1$) at week 24, with studies demonstrating a difference from placebo of about 3%. Previous phase II dose-ranging studies of LUM/IVA demonstrated modest reductions in sweat chloride (-9.5 mmol/L; 95% CI -15.1 to -3.9) for LUM 600 mg daily and -11.0 (95% CI -18.3 to -3.7) with LUM 400 mg twice daily.[18] This is a much smaller effect than what was observed with IVA therapy in G551D and R117H mutations (50 and 24 mmol/L, respectively).[11,19] The individual components of the drug were not included in phase III studies, so it is unknown to what degree each medication contributes to its efficacy. Results of the FDA analysis demonstrated a small FEV1 improvement similar to that for IVA monotherapy with a similar exacerbation rate ratio (0.6) those homozygous for the F508del CFTR mutation.[18] LUM monotherapy demonstrated a dose-dependent decrease in lung function and was not included as an arm in confirmatory studies, raising the concern of unknown biological plausibility of the combination of both agents resulting in significant improvements.[20]

A pre-specified hierarchical testing for key secondary endpoints was done to test for significance. If a test failed, all subsequent tests were considered not statistically significant. In TRAFFIC, the absolute change in $PPFEV_1$ from baseline was 2.2% , with a mean difference from placebo of 2.6% (95% CI 1.2 to 4.0) with LUM 400 mg/IVA twice daily. Similarly, in TRANSPORT, the change from baseline was 2.9% with a difference from placebo of 3.0% (95% CI 1.6 to 4.4). The mean difference versus placebo with the higher dose of LUM (600 mg twice daily) was 4.0% (95% CI 2.6 to 5.4) in TRAFFIC and 2.6 (95% CI 1.2 to 4.1) in TRANSPORT. Thirty nine percent of patients achieved a 5% or greater increase in the PPFEV1 (OR 2.22; $p<0.001$) compared to placebo. There was no significant difference in change in BMI in TRAFFIC, and therefore the remaining secondary endpoints were not tested and considered not significant. In TRANSPORT there was a statistically significant difference in change in BMI between LUM/IVA and placebo (0.4; 95% CI 0.2 to 0.5), but no statistically significant difference in absolute change in CFQ-R. The remaining secondary outcomes were not statistically significant. There was a nominal improvement in exacerbation rates in pooled data from TRAFFIC AND TRANSPORT with both doses of LUM/IVA compared to placebo (0.8 per 48 weeks vs. 1.14;RR 0.7; 95% CI 0.5-0.9 for LUM 600mg/IVA twice daily and 0.7 vs. 1.14; RR 0.61; 95% CI 0.4 to 0.8 for TRAFFIC and TRANSPORT, respectively, NNT 4-6), with a reduction in rate of about 34% compared to placebo. However, this is confounded by the other pre-modulation therapies received by patients. Sweat chloride or other biomarkers were not evaluated in the phase III trials. There does not seem to be a dose-response, as for many outcomes the combination including 400 mg LUM was more effective than 600 mg LUM.

Differences between these 2 studies and the study of IVA alone, which demonstrated no effect in this population, were duration (24 weeks vs. 16 weeks), the use of hypertonic saline was not allowed in the IVA trial, and lower baseline $PPFEV_1$ in the LUM/IVA trials. The FDA did not find evidence that LUM/IVA is superior to IVA alone with respect to improvement in $PPFEV_1$ and pulmonary exacerbations.[18]

Drug-drug interactions between LUM (a strong CYP3A inducer) and IVA (CYP3A substrate and weak inhibitor) necessitate higher doses of IVA. These properties also create potential difficulty with the fixed combination of these agents and may be one explanation for the numerically similar effect size of a 2-3% increase in $PPFEV_1$ seen with the combination compared to IVA alone.[21]

Clinical Safety:
Overall, any adverse event was reported in 95% of patients and it was generally well tolerated with low discontinuation rates. The most common adverse drug reactions that occurred in 5% of more of patients were generally respiratory and are included in the following table:

Table 1: Incidence of Adverse Drug Reactions in ≥5% of ORKAMBI-Treated Patients Who are Homozygous for the *F508del* Mutation in the *CFTR* Gene in 2 Placebo-Controlled Phase 3 Clinical Trials of 24 Weeks Duration		
Adverse Reaction (Preferred Term)	**ORKAMBI N=369 (%)**	**Placebo N=370 (%)**
Dyspnea	48 (13)	29 (8)
Nasopharyngitis	48 (13)	40 (11)
Nausea	46 (13)	28 (8)
Diarrhea	45 (12)	31 (8)
Upper respiratory tract infection	37 (10)	20 (5)
Fatigue	34 (9)	29 (8)
Respiration abnormal	32 (9)	22 (6)
Blood creatine phosphokinase increased	27 (7)	20 (5)
Rash	25 (7)	7 (2)
Flatulence	24 (7)	11 (3)
Rhinorrhea	21 (6)	15 (4)
Influenza	19 (5)	8 (2)

Serious adverse events were reported in 28.6% of patients in the placebo group and 22.8% of the patients in the LUM/IVA groups; infective pulmonary exacerbation was the most common serious adverse event observed (13% in pooled treatment group and 24.1% in placebo group). Minor elevations (> 3x the upper limit of normal range) of liver transaminases occurred 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 but were reported in 7 patients in the LUM/IVA group, of which 6 returned to baseline following discontinuation.

Withdrawals due to adverse events occurred at a higher percentage in the active treatment groups, but rates were low in all study arms.

Pharmacology and Pharmacokinetic Properties[22]:

Parameter	
Mechanism of Action	Improves the conformational stability of F508-del-CFTR, resulting in increased processing and trafficking of mature protein to the cell surface; facilitating increased chloride transport.
Oral Bioavailability	Exposure 3 times higher when administered with fat-containing foods compared to a fasting state.
Distribution and Protein Binding	Lumacaftor is 99% bound to plasma proteins, primarily albumin with a VD of 86L Ivacaftor is 99% protein bound, primarily to alpha 1-acid glycoprotein and albumin
Elimination	Majority of lumacaftor eliminated unchanged in feces. Majority of ivacaftor eliminated in feces after metabolic conversion.
Half-Life	25.2 hr (lumacaftor); 9 hr (ivacaftor)
Metabolism	Lumacaftor not extensively metabolized. Ivacaftor is primarily metabolized by CYP3A

Abbreviations:

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Weight Gain (BMI)
2) Mortality
3) Hospitalizations
4) Frequency of pulmonary exacerbations
5) Quality of Life and Pulmonary symptoms

Primary Study Endpoint:
1) Absolute change in PPFEV1 from baseline at week 24

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. TRAFFIC[1] Phase III, RCT, DB, PC, PG	1. LUM/IVA 600 mg Q24H / 250 mg Q12H 2. LUM/IVA 400 mg/ 250 mg Q12H 3. Placebo 24 weeks	Demographics: Homozygous for the *F508del-CFTR* mutation; mean baseline FEV1 61%; mean age 26 Key Inclusion Criteria: Sweat chloride >60 mmol/L or chronic sinopulmonary disease, FEV1 40-90% of predicted, ≥12 y/o Key Exclusion Criteria: Cirrhosis, portal HTN, risk factors for torsades de pointes, Hg < 10 g/dL, abnormal LFTs (≥3x ULN), GFR < 50 ml/min, QTcF > 450 msec, alcohol or drug abuse including cannabis, cocaine, and opiates, use of strong inhibitors, moderate inducers, or strong inducers of CYP3A4, pregnant or nursing females	mITT: 1. 185 2. 187 3. 187 Attrition: 1. 11 2. 10 3. 8	Change in $PPFEV_1$ from baseline: 1. 3.6 % 2. 2.2% 3. -0.44% Treatment difference: 1 vs. 3: 4.0%; 95% CI 2.6-5.4; p<0.001 2 vs. 3: 2.6%; 95% CI 1.2-4.0); p<0.001 Absolute change from baseline in BMI: 1. 0.35 kg/m2 2. 0.32 kg/m2 3. 0.19 kg/m2 Difference vs. placebo: NS Pulmonary Exacerbations : 1. 79 (43%) 2. 73 (40%) 3. 112 (61%) 1 vs. 3: RR 0.72; 95% CI 0.52-1.00; p=0.05* 2 vs. 3: RR 0.66; 95% CI 0.47 to 0.93; p=0.02* *Considered not significant due to statistical hierarchy	NA NA NS NA NA	Discontinuations due to Adverse Events: 1. 8 (4.4%) 2. 6 (3.3%) 3. 4 (2.2%) NS Serious Adverse Events: 1. 33 (18%) 2. 33 (18.1%) 3. 49 (26.6%)	NS NS	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: Selection: Low RoB; Appropriate randomization and allocation concealment; baseline characteristics similar Performance: Low RoB; Double-blind design; matching placebo Detection: Low RoB; site personnel, site monitor, and study team blinded Attrition: modified ITT analysis done using FAS including all randomized subjects who received any amount of study drug. Attrition overall low (<10%) and similar between grps. **Applicability**: Patient: Significant exclusion criteria limits generalizability to patient population; Only 58.1% on hypertonic saline and 64.5% on inhaled antibiotics Intervention: new fixed drug combination Comparator: Individual component comparator needed to assess contribution of LUM Outcomes: The literature remains uncertain on clinical outcomes best to assess gene therapy targeting the CFTR gene; Pulmonary exacerbations were defined as a new or change in antibiotic therapy for 4 or more of the following symptoms: new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10%; radiographic changes indicative of pulmonary infection Setting: Multinational (North America, Europe, Australia) **Analysis**: Good internal validity with little magnitude of effect and uncertain clinical significance. Funded by manufacturer.

2. TRANSPORT[1] Phase III, RCT, DB, PC, PG	1. LUM/IVA 600 mg/ 250 mg Q12H 2. LUM/IVA 400 mg/ 250 mg Q12H 3. Placebo 24 weeks	Demographics: Homozygous for the *F508del-CFTR* mutation; mean baseline FEV1 61%; mean age 26 Key Inclusion Criteria: Sweat chloride >60 mmol/L or chronic sinopulmonary disease, PPFEV1 40-90%, age ≥12 y Key Exclusion Criteria: Cirrhosis, portal HTN, risk factors for torsades de pointes, Hg < 10 g/dl, abnormal LFTs (≥3x ULN), GFR < 50 ml/min, QTcF > 450 msec, alcohol or drug abuse including cannabis, cocaine, and opiates, use of strong inhibitors, moderate inducers, or strong inducers of CYP3A4, pregnant or nursing females	ITT: 1. 187 2. 189 3. 187 FAS: 1. 185 2. 187 3. 187 Attrition: 1. 9 2. 15 3. 5	Change in $PPFEV_1$ from baseline: 1. 2.5 % 2. 2.9% 3. -0.15% Treatment difference: 1 vs. 3: 2.5%; 95% 1.2-4.1; p<0.001 2 vs. 3: 3.0%; 95% CI 1.6-4.4); p<0.001 Absolute change from baseline in BMI: 1. 0.48 kg/m2 2. 0.43 kg/m2 3. 0.07 kg/m2 Treatment Difference: 1 vs. 3: 0.41; 95% CI 0.23-0.59; p<0.001 2 vs. 3: 0.36; 95% CI 0.17-0.54; p<0.001 Pulmonary Exacerbations (Rate Ratio): 1. 94 (51%) 2. 79 (42%) 3. 139 (74%) 1 vs. 3: RR 069; 95% CI 0.52-0.92; p=0.01* 2 vs. 3: RR 0.57; 95% CI 0.42 to 0.76; p=<0.001* *Considered not significant due to statistical hierarchy	NA NA NA NA ARR 23/ NNT 5 ARR 32/ NNT 4	Discontinuations due to Adverse Events: 1. 6 (3.2%) 2. 11 (5.9%) 3. 2 (1.1%) Serious Adverse Events: 1. 51 (27.4%) 2. 31 (16.6%) 3. 57 (30.6%)	NS NS	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: Selection: Low RoB; Appropriate randomization and allocation concealment; baseline characteristics similar Performance: Low RoB; Double-blind design; matching placebo Detection: Low RoB; Site personnel, site monitor, and study team blinded Attrition: modified ITT analysis done using FAS including all randomized subjects who received any amount of study drug. Attrition overall low (<10%) and similar between groups. **Applicability**: Patient: Significant exclusion criteria limits generalizability to patient population; Only 58.1% on hypertonic saline and 64.5% on inhaled antibiotics Intervention: OK Comparator: Individual component comparator needed to assess contribution of LUM Outcomes: Unclear on clinical outcomes best assess gene therapy targeting the CFTR gene. Pulmonary exacerbations were defined as a new or change in antibiotic therapy for 4 or more of the following symptoms: new or increased hemoptysis; increased cough; increased dyspnea; malaise, fatigue, or lethargy; temperature above 38°C; anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10%; radiographic changes indicative of pulmonary infection Setting: Multinational (North America, Europe, Australia) **Analysis**: Good internal validity with little magnitude of effect and uncertain clinical significance. Funded by manufacturer.

Abbreviations [alphabetical order]: ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; CFTR = Cystic Fibrosis Transmembrane Conductance Regulator; FAS = full analysis set; GFR = glomerular filtration rate; Hg = hemoglobin; HTN = hypertension; mITT = modified intention to treat; IVA = ivacaftor; LUM= lumacaftor; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; $PPFEV_1$ = percent-predicted forced expiratory volume in one second; RCT = randomized controlled trial; RoB = risk of bias; ULN = upper limit of normal; y = years.

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Appendix 1: Highlights of Prescribing Information

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

ORKAMBI™ (lumacaftor/ivacaftor) tablets, for oral use
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------

ORKAMBI is a combination of lumacaftor and ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, indicated for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *F508del* mutation on both alleles of the *CFTR* gene. (1)

Limitations of Use:
The efficacy and safety of ORKAMBI have not been established in patients with CF other than those homozygous for the *F508del* mutation. (1)

----------DOSAGE AND ADMINISTRATION----------

- Adults and pediatric patients age 12 years and older: two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours. (2.1)
- Reduce dose in patients with moderate or severe hepatic impairment. (2.2, 8.6, 12.3)
- When initiating ORKAMBI in patients taking strong CYP3A inhibitors, reduce ORKAMBI dose for the first week of treatment. (2.3, 7.1, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: lumacaftor 200 mg and ivacaftor 125 mg. (3)

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Use in patients with advanced liver disease: ORKAMBI should be used with caution in these patients and only if the benefits are expected to outweigh the risks. If ORKAMBI is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced. (2.2, 5.1, 6.1)
- Liver-related events: Elevated transaminases (ALT/AST) have been observed in some cases associated with elevated bilirubin. Measure serum transaminases and bilirubin before initiating ORKAMBI, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Interrupt dosing in patients with ALT or AST >5 x upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN. Following resolution, consider the benefits and risks of resuming dosing. (5.2, 6.1)
- Respiratory events: Chest discomfort, dyspnea, and respiration abnormal were observed more commonly during initiation of ORKAMBI. Clinical experience in patients with percent predicted FEV_1 ($ppFEV_1$) <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy. (5.3, 6.1)
- Drug interactions: Use with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index may decrease systemic exposure of the medicinal products and co-administration is not recommended. Hormonal contraceptives should not be relied upon as an effective method of contraception and their use is associated with increased menstruation-related adverse reactions. Use with strong CYP3A inducers may diminish exposure of ivacaftor, which may diminish its effectiveness; therefore, co-administration is not recommended. (5.4, 6.1, 7, 12.3)
- Cataracts: Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor, a component of ORKAMBI. Baseline and follow-up examinations are recommended in pediatric patients initiating ORKAMBI. (5.5)

----------ADVERSE REACTIONS----------

The most common adverse reactions to ORKAMBI (occurring in ≥5% of patients with CF homozygous for the *F508del* mutation in the *CFTR* gene) were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, blood creatine phosphokinase increased, rash, flatulence, rhinorrhea, influenza. (6.1)

----------DRUG INTERACTIONS----------

See Full Prescribing Information for a complete list. (2.3, 7, 12.3)

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

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

Revised: 07/2015

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:

- No preferred alternatives at this time

Approval Criteria		
1. Is this a request for continuation of therapy (patient already on ivacaftor or lumacaftor/ivacaftor)?	Yes: Go to **Renewal Criteria**	No: Go to #2
2. What is the diagnosis?	Record ICD-10 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?	Document and go to #5 If no baseline, request a baseline value before approving therapy	
5. Is the request for ivacaftor (Kalydeco)?	**Yes:** Go to #6	**No:** Go to #10
6. What is the patient's baseline sweat chloride level?	Document and go to #7. If no baseline level, Request a baseline level before approving therapy.	
7. Does the client 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	**Yes:** Go to #14	**No:** Go to #9 If unknown, there needs to be a FDA cleared CF mutation test to detect the presence of the CFTR mutation prior to use.

test?		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 cleared 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 (Orkambi)?	**Yes:** Go to #11	**No:** Pass to RPH; Deny (medical appropriateness)
11. Does the client have a diagnosis of cystic fibrosis and is 12 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-cleared CF mutation test?	**Yes:** Go to #13	**No:** Pass to RPH; Deny (medical appropriateness) If unknown, there needs to be a FDA cleared 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?	**Yes:** 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	**Yes:** Go to #15	**No:** Pass to RPH; Deny (medical appropriateness)

(<6 y/o) and normal lung function?: • Dornase alfa, AND • Hypertonic saline, AND • Inhaled or oral antibiotics (if appropriate)		
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 tests (within previous 3 months)?	Document and go to #17. If no baseline, request baseline before approving.	
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 (Kalydeco): **a.** Does the patient have a documented physiological response to therapy and evidence of adherence after 30 days of treatment as defined as a sweat chloride test that has decreased by at least 20 mmol/L from baseline?	**Yes:** Go to #7	**No:** Go to #3
3. If the prescription is for lumacaftor/ivacaftor (Orkambi): a. Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider	**Yes:** Go to #7	**No:** Pass to RPH; 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

assessment?		medical appropriateness.
4. Does the patient have documented response to therapy as defined as below? For patients ≥ 6 y/o • An improvement or lack of decline in lung function as measured by the FEV_1 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 2-5 y/o (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
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 and go to #7. Note: Therapy should be interrupted in patients with AST or ALT >5 x the upper limit of normal, or ALT or AST >3 x upper limit of normal with bilirubin > 2 x the upper limit of normal.	
7. Is the CFTR modulator dosed appropriately based on age, weight, and co-administered drugs (See dosing and administration below)?	**Yes:** Approve for additional 4 months (total of 6 months since start of therapy)	**No:** Pass to RPH; Deny (medical appropriateness)

Dosage and Administration:

Ivacaftor:

- Adults and pediatrics ≥6 y/o: 150 mg orally every 12 hours with fat-containing foods
- Children 2 to < 6 y/o:
  - < 14 kg: 50 mg packet every 12 hours
  - ≥ 14 kg: 75 mg packet every 12 hours
- Hepatic Impairment
  - Moderate Impairment (Child-Pugh class B):
    - ≥6 y/o: one 150 mg tablet once daily
    - 2 to < 6 y/o 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

Lumacaftor/ivacaftor:

- Adults and pediatrics ≥12 y/o: Two tablets (lumacaftor 200 mg/ivacaftor 125 mg) every 12 hours
- Hepatic Impairment
  - Moderate Impairment (Child-Pugh class B):
    - Two 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/DUR Review: *11/15 (MH); 7/15; 5/15; 5/14; 6/12*
Implementation: ***TBD****; 9/15; 8/12*